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Adherence to latent tuberculosis treatment among immigrants in low endemic settings: a scoping review

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Résumé

Contexte : En dépit du fait que la tuberculose est un problème de santé publique important dans les pays en voie de développement, les pays occidentaux doivent faire face à des taux d'infection important chez certaines populations immigrantes. Le risque de développer la TB active est 10% plus élevé chez les personnes atteintes de TB latente si elles ne reçoivent pas de traitement adéquat. La détection et le traitement opportun de la TB latente sont non seulement nécessaires pour préserver la santé de l'individu atteint mais aussi pour réduire le fardeau socio-économique et sanitaire du pays hôte. Les taux d'observance des traitements préventifs de TB latente sont faibles et une solution efficace à ce problème est requise pour contrôler la prévalence de l'infection. L'objectif de ce mémoire est d'identifier les facteurs qui contribuent à l'observance thérapeutique des traitements de TB latente auprès de nouveaux arrivants dans les pays occidentaux où les taux endémiques sont faibles.

Méthodologie : Une revue systématique a été effectuée à partir de bases de données et répertoires scientifiques reconnus tels *Medline, Medline in Process, Embase, Global Health, Cumulative Index to Nursing, le CINAHL* et la librairie *Cochran*e pour en citer quelques un. Les études recensées ont été publiées après 1997 en français, en anglais, conduites auprès de populations immigrantes de l'occident (Canada, États-Unis, Europe, Royaume-Uni, Australie et la Nouvelle Zélande) dont le statut socio-économique est homogène.

Résultats : Au total, neuf (9) études réalisées aux États-Unis sur des immigrants originaires de différents pays où la TB est endémique ont été analysées: deux (2) études qualitatives ethnographiques, six (6) quantitatives observationnelles et une (1) quantitative interventionnelle. Les facteurs sociodémographiques, les caractéristiques individuelles, familiales, ainsi que des déterminants liés à l'accès et à la prestation des services et soins de santé, ont été analysés pour identifier des facteurs d'observance thérapeutique. L'âge, le nombre d'années passées dans le pays hôte, le sexe, le statut civil, l'emploi, le pays d'origine, le soutien familiale et les effets secondaires et indésirables du traitement de la TB ne sont pas des facteurs

déterminants de l'adhésion au traitement préventif. Toutefois, l'accès à l'information et de l'éducation adaptées aux langues et cultures des populations immigrantes, sur la TB et des objectifs de traitement explicites, l'offre de plan de traitement plus court et mieux tolérés, un environnement stable, un encadrement et l'adhésion au suivi médical par des prestataires motivés ont émergés comme des déterminants d'observance thérapeutique.

Conclusion et recommandation : Le manque d'observance thérapeutique du traitement de la TB latente (LTBI) par des populations immigrantes, qui sont déjà aux prises avec des difficultés d'intégration, de communication et économique, est un facteur de risque pour les pays occidentaux où les taux endémiques de TB sont faibles. Les résultats de notre étude suggèrent que des interventions adaptées, un suivi individuel, un encadrement clinique et des plans de traitement plus courts, peuvent grandement améliorer les taux d'observance et d'adhésion aux traitements préventifs, devenant ainsi un investissement pertinent pour les pays hôtes.

Mots-clés : tuberculose, prévention, traitement, immigrants

Abstract

Background: While the burden of tuberculosis (TB) is greatest in developing countries, industrialized nations are increasingly confronted with imported TB found primarily among immigrants from TB-endemic nations. Latent TB infection (LTBI), whereby the TB bacterium is dormant, is associated with a 10% risk of developing active TB disease if left untreated. Treatment of LTBI is important not only to safeguard the future health of infected individuals, but also to reduce the subsequent human and financial toll on the host country. Adherence and completion of preventive treatment for LTBI is poor and addressing this problem is crucial to controlling the prevalence of TB. The aim of the proposed paper is to identify the determinants associated with adherence to LTBI treatment among the foreign-born population residing in low TB-endemic, immigrant-receiving countries.

Methods: A scoping review was performed using Medline, Medline in Process and Other Non-Indexed Citations, Embase, Global Health, Cumulative Index to Nursing and Allied Health Literature (CINAHL), as well as the Cochrane Library. Studies were limited to those published in English and French since 1997, involving adults over 18 years of age, conducted in immigrant-receiving counties (Canada, the United States, Europe, Australia and New Zealand), with comparable socio-economic levels.

Results: In total, nine studies conducted in the United States (US) originating from various TB-endemic countries were included in the analysis: two qualitative ethnographic, six quantitative observational and one quantitative interventional. Socio-demographic factors, characteristics relating to the affected individuals and their families, as well as factors relating to organization and delivery of healthcare delivery, were analyzed to identify determinants of adherence. Age, years of stay in the US, sex, marital status, occupation, country of origin, family support and drug-related side effects did not appear to be significant determinants of adherence or completion of preventive treatment. However, culturally- and linguistically-sensitive education about the disease and treatment objectives, the selection of well-tolerated short treatment schedules, stable environment, and support and regular assessment from dedicated healthcare providers emerged as significant determinants of adherence and treatment completion.

Conclusion and recommendations: Lack of adherence to prescribed treatment for LTBI by immigrants, who are already struggling with problems of integration, communication and economic hardship, is a growing threat in low TB-endemic, immigrant-receiving countries. Our findings suggest that interventions such as culturally congruent education, individually tailored assessment and support by healthcare providers and short treatment regimens can considerably improve the likelihood of treatment completion and appear to be worthwhile investments for the host country.

Keywords : tuberculosis, prevention, treatment, immigrants

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ATS :	American Thoracic Society
BCG vaccine :	Bacille Calmette-Guérin vaccine
CDC :	Centers for Disease Control and Prevention
CI :	Culturally-relevant intervention
CINAHL :	Cumulative Index to Nursing and Allied Health Literature
DOPT :	Directly observed preventive treatment
DOT :	Directly observed treatment
DOTS :	Directly observed treatment, short-course
EDM :	Electronic monitoring devices
EM :	Explanatory model
HIV :	Human immunodeficiency virus
IDSA :	Council of the Infectious Diseases Society of America
IGRA :	Interferon-gamma release assay
INH :	Isoniazid
KAB :	Knowledge, attitude and belief
LTBI :	Latent tuberculosis infection
MDR-TB :	Multi-drug resistant tuberculosis
MECIR :	Methodological Expectations of Cochrane Intervention Reviews
MEMS :	Medication event monitoring system
MMWR :	Morbidity and Mortality Weekly Report
MTB :	Mycobacterium tuberculosis bacilli
PHN :	Public health nurse
PRHC :	Philadelphia Refugee Health Collaborative
PZA :	Pyrazinamide
RFB :	Rifabutin
RHAP :	San Diego Refugee Health Assessment Program
RIF :	Rifampin
RMP :	Rifampicin
RPT :	Rifapentine

SAT :	Self-administered treatment
TB :	Tuberculosis
TLTBI :	Treatment of latent tuberculosis infection
UN :	United Nations - Ref: (UN, 2013). UN not defined in paper
WHO :	World Health Organization

Dédicace

To the "guardian angels" who have guided me along this journey – you have been a blessing in my life more than you will ever know.

To those whose trajectory leads to a new life abroad ... know that the challenges you face have not gone unnoticed. Your health and well-being will always be important.

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Introduction

As the primary cause of global morbidity and mortality due to an infectious agent, tuberculosis (TB) continues to be a major health problem worldwide (MacPherson and Gushulak 2006). According to a 2014 Global TB Report published by the World Health Organization (WHO), an estimated 9 million new cases of TB were reported in 2013 – most originating in Southeast Asia and the Western Pacific. Moreover, one-third of the world's population has been diagnosed with a latent TB infection. The risk of reactivation among those diagnosed with latent TB and no other risk factors is approximately 10% per lifetime. Yet, among infected individuals with an impaired immunity, the risk of developing active TB is significantly increased to 10% per year (Lin and Flynn 2010).

With an ever-shifting global population, industrialized nations are experiencing a rising immigrant population originating from TB-endemic nations. Consequently, imported TB is found among this vulnerable population (Levesque et al. 2004, Parsyan et al. 2007). In 2012, the foreign-born population in Canada, which represents 24% of the total population, accounted for 65% of all reported TB cases, with an incidence rate of 13,4 per 100 000 population. In contrast, the Canadian-born non-aboriginal population accounted for a significantly lower percentage of reported cases at 10%, with an incidence rate of 0,7 per 100,000 population (Public Health Agency of Canada 2012). Indeed, foreign-born individuals, particularly those from TB-endemic countries, represent a significant proportion of the total number of reported TB cases. Low-incidence, immigrant-receiving nations have identified latent TB treatment as a vital component to prevent and, ultimately, eliminate TB (Golub et al. 2006).

In light of the heightened risk of reactivation among foreign-born men and women, adherence to latent TB treatment is among one of the TB control strategies that have been underscored. Indeed, once a patient has completed screening and treatment has been initiated, adherence to therapy is a challenge of critical importance to TB control strategies.

Examining adherence and associated factors

The asymptomatic nature of a latent tuberculosis infection (LTBI) is, in itself, an issue to ensure adherence to a given treatment regimen. While isoniazid (INH) is the recommended first-line LTBI treatment, poor adherence to this and other anti-tuberculous medications prevails as a major obstacle to TB control, thereby increasing the risks of drug resistance, morbidity and mortality at both individual and community levels (WHO 2003). The Centers for Disease Control and Prevention (CDC), define adherence to treatment as a patient's compliance with a recommended course of treatment such that he/she takes all medications as prescribed for the entire length of time necessary. However, several factors may influence a patient's ability to adhere to a preventive treatment regimen (CDC 2013). Indeed, it has been found that interventions and programs designed to aid immigrants adhere to LTBI treatment programs are not sensitive enough to their unique context, thus demonstrating the relevance of contextual factors encompassing a given individual as they relate to adherence to LTBI treatment. While therapy- and condition-related factors impact adherence to LTBI treatment within the biomedical scope, various determinants related to the specific context of patients have been identified as influencing adherence to latent TB treatment. Consequently, a multifaceted approach to patient care has been emphasized, prompting patient-centered approaches with patient-centered treatment priorities (Coreil et al. 2004). Furthermore, in order to improve the effectiveness of LTBI treatment, culture-based approaches have been emphasized as a means of focusing on the needs of patients as well as their communities (LoBue and Moser 2003, Cangelosi et al. 2004, Parsyan et al. 2007).

Definition of the problem and objective

TB is a significant public health problem and is a primary cause of global morbidity and mortality. In low TB-endemic regions, the disproportionate burden of LTBI among immigrants underscores the importance of TB control measures to reduce the risk of active TB. Moreover, the HIV pandemic as well as the heightened risk of transmission in congregate settings such as healthcare facilities, correctional facilities and homeless shelters increase the complexity to

effectively prevent and control TB, thereby justifying its relevance as an important public health problem, necessitating attention from policy makers and health practitioners alike.

Although diagnosis and treatment of active TB is the first priority, measures to effectively screen and treat individuals with LTBI is an important second priority. Screening is a means of TB control with the aim of identifying individuals at increased risk of progressing to active TB for whom treatment will be most beneficial (Canadian Thoracic Society 2013). Other "systems put in place to deal with illness" as per the Commission on Social Determinants of Health, include efforts to increase health promotion and healthcare access by way of treatment support, active case finding, outreach services for high risk populations such as migrants (Hargreaves et al. 2011). While screening and the aforementioned TB control efforts are vital, treatment of LTBI, and specifically adherence to treatment, is a critical public-health measure to be taken into consideration and is indeed the focus of this thesis. Poor adherence to LTBI treatment is a significant public-health problem particularly among migrants within low TB-endemic developed regions. The public-health challenge to TB control is embedded within the various social determinants of health that influence the means of effectively treating LTBI, specifically within the migrant context. It is imperative to adopt a social determinant of health perspective and acknowledge these factors within the migrant context in order to effectively address possible weaknesses in current immigrant healthcare policies. Accordingly, this issue provides a motive for researchers, healthcare providers and policy makers alike to delve into the context of adherence to latent TB treatment in order to further understand the factors and processes unique to immigrants. Recent appeals for further research and discussions relating to the complexities of adherence to LTBI treatment regimens have underscored the necessity of defining the integral components of treatment completion among an immigrant population.

The objective of this study is to identify the determinants that influence adherence to latent TB treatment among the adult foreign-born population residing in low TB-endemic, immigrant-receiving countries, by way of a scoping review of interventional and observational studies. In effect, the present review is aimed at providing a significant scope of the factors that influence adherence to LTBI treatment as it will enable healthcare providers to acquire a heightened awareness and understanding of the factors that influence immigrants' adherence to latent TB treatment at the level of the patient, the healthcare provider and the clinic.

Chapter 1: Literature Review

1.1 Tuberculosis – Aetiology and pathogenesis

Tuberculosis (TB) is an infectious disease caused by the bacteria *mycobacterium tuberculosis*. Infection of the TB bacterium does not imply that an individual has tubercular disease. While the latter refers to the active state of the TB bacterium, latent tuberculosis infection (LTBI) is the asymptomatic, non-contagious, latent form of TB (CDC 2012).

Active TB commonly presents as pulmonary TB (in the lungs). In some cases, tubercular disease can occur outside the lungs, known as "extra-pulmonary TB", whereby the active TB bacterium is found in the bones, joints, central-nervous, lymphatic and/or circulatory systems. Pulmonary and systemic symptoms include prolonged cough, blood-tinged sputum, chest pain, weight loss, fever, night sweats, fatigue and chills, respectively. Active TB is an airborne infectious disease. When individuals with active pulmonary TB and/or laryngeal TB cough, sneeze or speak, they expel the TB bacterium, in the form of droplet nuclei, into the air, which may be inhaled by any close contact (CDC). The probability of transmission depends on several factors, including the virulence of the mycobacterium strain, the number of droplet nuclei expelled by the active TB case, the duration of exposure, the proximity between the active case and the close contact, the presence and effectiveness of ventilation, the level of immunity of the close contact and delays in diagnosis and/or effective treatment (CDC, Canadian Thoracic Society 2013).

1.2 Latent TB infection

Latent TB is a clinical condition lacking clinical or radiological signs of the tubercular disease whereby the TB bacterium is dormant within the body (Reichman 2006). Mycobacterium TB is able to persist in humans for long periods without clinical disease. Chronic persistence within the body may involve alterations in the TB bacterium's metabolic processes which slow down, arrest and may remain in this state for years. This adaptive bacterial response could be one factor determining the ability of the bacteria to enter into a dormant state (Rustad et al. 2009).

Although the TB bacterium can remain inactive for several months, years or decades, individuals have a risk of approximately 10% to develop TB in their lifetime in the absence of a complete treatment for LTBI. Of those, 5% have a heightened risk to develop early primary TB soon after infection by the TB bacterium, while the remaining half have a greater risk of TB reactivation years later following infection (Canadian Thoracic Society 2013). Yet, the percentage varies considerably with age and other risk factors. Infants, young children and the elderly are at an increased risk of contracting primary TB on account of their weakened immunity. In 2012, children under 15 years of age accounted for an estimated 530 000 TB cases and 74 000 TB deaths worldwide (WHO 2013).

Furthermore, several conditions hinder the immune system, thereby significantly facilitating primary or reactivation TB. Individuals infected with HIV have a high risk of developing TB. Indeed, those with an HIV and TB co-infection have approximately a 10% annual risk of developing TB and are 30 times more likely to develop active TB disease than individuals without HIV (WHO, Merck). An estimated 1,1 million HIV-positive individuals developed TB in 2012, which resulted in 320,000 deaths (WHO, 2013). As a consequence of the HIV pandemic, TB incidence and mortality have significantly increased over the past 20 years. Indeed, HIV/TB co-infection has been found to have a higher mortality rate than either HIV or TB alone (Piggott and Karakousis 2011). Among individuals with LTBI, HIV is the most significant risk factor for progression to active TB. However, treatment of LTBI with INH has been found to be highly effective in preventing development of active disease among HIV-infected individuals. In a 2010 meta-analysis of randomized controlled trials, Akolo et al. found that TB prophylaxis reduced the incidence of active TB by over 30% among HIV-infected persons. Furthermore, prevention of active TB in HIV-positive patients has also been achieved among those on highly active antiretroviral therapy (HAART) whereby TB incidence was reduced by up to 90% compared to those not receiving antiretroviral drugs (Girardi, et al. 2005). Although the HIV/TB co-infection is particularly prevalent in limited resource settings, its risk is still significant in developed countries with an increasing proportion of LTBI among migrant populations. In a recent study conducted by Rivest, Sinyavskaya & Brassard (2014), the authors found that among 33 HIV-positive TB cases, 29 (87.9%) were foreign born, originating from the HIV-endemic regions of Sub-Saharan Africa and the Caribbean. Other immunocompromised conditions that facilitate TB development include diabetes, malnutrition, head and neck cancer,

gastrectomy, jejunoileal bypass surgery, end-stage renal disease and silicosis. Chronic immunosuppressive drugs such as corticosteroids and TNF-inhibitors have also been found to promote TB. Moreover, long-term substance abuse such as injection drug use, alcohol and smoking are significant detriments to the immune system and further increase the risk to develop TB. As well, certain vulnerable populations diagnosed with LTBI have a heightened risk to reactivate. They include migrants as well as individuals who live or work in settings with a high prevalence of TB, such as homeless shelters, hospitals, nursing homes and prisons (CDC 2013). Also, the risk of reactivation TB is significant among immigrants diagnosed with LTBI from countries with a high incidence of TB. More than half of all adults originating from TB-endemic countries have LTBI. If an adult migrates to another country, the risk of TB reactivation is highest within the first five years of arrival and remains a significant risk for several years compared to the native low-prevalent population (Frothingham et al. 2005).

Although high-risk populations such as migrants, inmates, the homeless and drug users have a greater vulnerability to develop active TB, each within their own unique context is influenced by certain social determinants and is shaped by unique experiences that impact their health. Should high-risk populations be taken into consideration as a whole, one will undermine the social determinants of health unique to each of these groups. As such, the focus of this thesis is specifically among the migrant population in order to underscore the social determinants unique to these individuals that influence adherence to LTBI treatment. Adopting a broader scope of the social determinants that challenge the health of migrants has provided the opportunity to appreciate the challenges faced by them.

1.3 Epidemiology of TB

As the second leading cause of death following the human immunodeficiency virus (HIV), TB continues to be a significant health problem worldwide. According to a 2013 Global TB Report published by the World Health Organization (WHO), an estimated 8,6 million incident cases were reported in 2012 (WHO, 2013). Most of these incident cases originated in the Southeast Asian, Western Pacific regions, as well as the African regions, accounting for 58% and 27% of global TB cases, respectively. India, China, South Africa, Indonesia and Pakistan experienced the largest number of incident cases in 2012, while India comprised more than a

quarter of the cases worldwide. At present, TB incidence rates are on the decline globally. The European regions experienced the fastest decline in TB incidence rates at 6.5% annually, while the slowest rates were in the Eastern Mediterranean and Southeast Asian regions at less than 1% and 2%, per year, respectively.

Since 1990, the global prevalence rate decreased by 37% such that there were an estimated 12 million prevalent cases in 2012. According to the WHO, a non-uniform declining trend was reported in estimated prevalent TB case rates in the regions of Africa, the Americas, Eastern Mediterranean, Europe, Southeast Asia and the Western Pacific (WHO, 2013). Presently, while the prevalence rates in the Americas were lowered by 50% compared to their baseline in 1990, the African and Eastern Mediterranean regions have not achieved such a significant decline.

Furthermore, an estimated 1,3 million deaths were attributed to TB in 2012. HIV-negative individuals accounted for 940,000 deaths, while approximately 4% of TB deaths occurred among those living with HIV. The African and Southeast Asian regions reported nearly 75% of total TB deaths, a third of which were evidenced in India and South Africa. High-income, industrialized countries such as Canada, the US, Australia and New Zealand, reported low TB deaths per 100,000 population as compared to low-income, TB-endemic countries in the regions of Africa and Asia, with TB deaths as high as 40 per 100,000 population (WHO, 2013).

1.4 Effect of migration on TB

The epidemiology of TB among low-endemic developed regions reflects a similar underlying shift whereby the incidence of TB among the foreign-born population is increasing in contrast to that of the native population, whose TB incidence is decreasing. This disparity is attributed primarily to an interaction between an increasing immigrant population, particularly among immigrants from TB-endemic countries, and the reactivation of a latent TB infection (LTBI) acquired prior to immigration (Pareek et al. 2012). Indeed, as previously mentioned, a significant proportion of TB cases among foreign-born individuals occurs within the first five years after arrival as reflected in surveillance data from low-endemic industrialized countries. In order to ascertain the context in its entirety, it is imperative to understand international migration

trends. Specifically, insight into the dynamic migration pattern of international migrants over the past two decades will enable a better understanding of its impact on tuberculosis case rates in the developed regions and, in particular, the presence of imported TB found among this vulnerable migrant population (Pareek et al. 2012).

Migration can be defined as "the process of going from one country, region or place of residence to settle in another" short term or long term (Bhugra and Becker 2005). Reasons for migration are political, social, and economic whether it be to escape persecution, to seek a better quality of life or to acquire greater financial opportunity.

As immigrants attempt to adjust to a new country, they face several challenges. Bhugra and Becker noted that migration involves significant losses as immigrants are uprooted from their native land. The loss of cultural values, self-identify, social structures and support networks are salient and significantly impact this vulnerable population. In 2013, there were 232 million international immigrants, including both foreign-born and foreign citizens, worldwide (UN, 2013). Of these, 59% lived in the developed nations, yet mostly originated from a developing region. As per the International Migration Report published by the United Nations (UN), developed regions comprise all countries of Europe, North America, Australia, New Zealand and Japan, while developing regions refer to all countries of Africa, Asia (excluding Japan), Latin America and the Caribbean, as well as Melanesia, Micronesia and Polynesia.

Between 1990 and 2013, there was a significant increase of 77 million international immigrants. Of these, 69% migrated to the developed regions, more than three-quarters of them born in a developing region. North America experienced the largest gain in the absolute number of international immigrants during that period with a growth of 25 million, followed closely by Europe at 23 million. The majority of those who migrated to North America and Europe originated from Latin America, the Caribbean, Asia and Africa. Between 1990 and 2013, the US experienced the largest increase with approximately 23 million migrating during that period. By 2013, one-fifth of the world's total international immigrants lived in the US, the largest number of immigrants in a country or area. Moreover, that same year, three-quarters of all international immigrants were between 20 to 64 years of age, while 25 million were aged 65 years or older.

As per the WHO (WHO Constitution 1948), health may be defined as a state of complete physical, mental and social well-being. Yet within that scope one must acknowledge and address the structural inequalities these mobile populations face as they attempt to adjust to a new country. Indeed various social determinants of health experienced by migrants significantly impact their health. These include reasons for migrating, the migration process itself, language skills, race and legal status to name a few. Moreover, different categories of migrants may have diverse experiences throughout their journey, making them susceptible to various factors that may negatively impact their health. The migration process in itself has three phases, including pre-departure, transit and arrival, each phase posing different challenges and risk factors. Indeed, Bhugra and Becker (2005) noted that migration involves significant losses as immigrants are uprooted from their native land. The loss of cultural values, self-identity, social structures and support networks are salient and significantly impact this vulnerable population. In addition, often confronted by barriers to health and social services, migrants' health is further undermined as they experience various social inequalities. Ultimately, various structural factors at the macro, intermediate and individual levels have been documented within the context of migration. For example, a low socio-economic status of some migrants, limited social capital, stressors unique to the migration context, loss of cultural beliefs and decrease use of health services (International Organization for Migration 2006).

When studying the spectrum of illnesses in international immigrants seen in clinics across North America, Europe and Australia between 1997 and 2009, McCarthy et al. noted that one-third of immigrants had TB (latent or active) with LTBI being the most common (24% of adults and 11% of children; McCarthy et al. 2013). Of special interest, 29% of the active TB cases were detected five years after arrival. Healthcare providers should use any opportunity to ask questions such as place of birth, current and past place(s) of residence and places travelled so that medical care can be approached through globally mobile populations, ensuring that immigrants and their health disparities are appropriately addressed. However, various countries may address migrants' health needs differently. Each of their approaches toward these mobile populations differ based on existent policies whereby various factors, including patterns of migration, migrants entering the country, as well as the type of welfare state and legal system come into consideration. Moreover, the extent to which policies are implemented in practice and to which various providers are well informed of their stipulations, remains unclear. For instance,

as criticized by NGOs in Italy, the implementation of the law stipulating health coverage for all migrants regardless of legal documentation, varies based on region and health center. In Germany, though provision of care to undocumented migrants exists, they have no access to the formal health system since legal employment and residence status are requisites for eligibility (Platform for International Cooperation on Undocumented Migrants 2007).

Most immigration-related TB screening is directed toward the detection of active TB. The detection and treatment of LTBI has not been a major focus in many developed countries, though rates of LTBI are high in migrant groups and consequently reactivation of TB is inevitable. This fact is well documented in nations with well-established departure screening. Consequently, transmission of TB does occur among foreign-born migrants after arrival in certain defined socio-economic and cultural settings, including high-risk clusters, such as homeless people, alcoholics and within migrant communities themselves (MacPherson and Gushulak 2006).

Furthermore, the healthcare needs of certain migrant groups, including undocumented migrants or asylum-seekers, may not be addressed as their access to essential health care may be restricted (WHO 2008). Beyond the scope of accessibility, various social, cultural, structural, linguistic, gender, financial and geographical determinants influence the availability, acceptability and quality of health services offered to migrants (PICUM 2007). Indeed, migrants are rarely included in the development of services targeted at their unique needs. Consequently, healthcare services may not be sensitive to the different cultures, languages, and migratory experiences of these displaced populations, ultimately hindering the diagnosis and appropriate treatment of migrants (Bhugra and Becker 2005). Moreover, many immigrant communities are unaware of the healthcare services available attesting to their underutilization by this mobile population (PICUM 2007).

As foreign-born immigrants comprise the majority of the LTBI population, the knowledge attitude and beliefs (KAB) of this segment regarding TB is of critical significance as it may influence their use of health services. When comparing US-born with foreign-born immigrant LTBI patients, Colson et al. noted that foreign-born immigrants were less likely to acknowledge that they had LTBI and felt more “protected” from developing TB (Colson et al.

2010). Better understanding of foreign-born patients' KAB may contribute to reduction of barriers and improved treatment outcome.

In summary, given a dynamic global population, imported TB has become a significant concern among developed countries. Low incidence, immigrant-receiving nations have identified LTBI treatment as a vital component to prevent and ultimately eliminate TB (Menzies et al. 2005, Ailinger et al. 2006, Golub et al. 2006). If the objective of completing LTBI treatment is achieved, the number of individuals who progress to active TB is significantly reduced (Canadian Lung Association, 2000). Yet before one can address factors that may impact adherence to treatment, it is essential to identify the different treatment regimens available that in themselves may be a barrier to adherence.

1.5 Latent TB treatment

Treatment for LTBI is an essential component of TB control at large. However, prior to treating LTBI, active TB must be ruled out so as to avoid inadequately treating the disease and heightening the risk of developing drug-resistant strains. Nonetheless, once LTBI is confirmed, isoniazid (INH) is the first-line anti-tuberculous medication recommended in light of its effectiveness and relative safety (Schwartzman 2002).

A randomized controlled trial to investigate INH treatment duration highlighted the effectiveness of INH as a function of adherence and duration of treatment. Researchers found that "with daily INH for 1 year, >80% compliance, gave 93% protection, and 60-68% compliance gave 49% protection. With daily INH for 6 months, >80% compliance, gave 69% protection" (WHO 1982). Comstock subsequently reviewed controlled trials on duration of treatment and concluded that 6 months of INH does not provide optimal prevention, and 12 months of preventive treatment does not provide additional protection from TB (Comstock 1999). The author did find that optimal prevention was achieved by nine to ten months of INH treatment. Thus, 300 mg of daily INH for nine months is the recommended treatment for LTBI (American Thoracic Society 2000).

Yet, alternative INH treatment regimens for adults have been suggested as a means of addressing issues relating to side effects and adherence to treatment. One consists of nine months

of daily dose of INH (5 mg/kg with maximum dose of 300 mg) or nine months, twice weekly (15 mg/kg with maximum dose of 900 mg). Alternatively, six months of INH daily may be recommended (5 mg/kg with maximum dose of 300 mg) OR twice weekly (15 mg/kg). Indeed, while the nine-month treatment regimen has demonstrated to be more effective, the six-month course was noted to be more cost effective and patients may adhere to a shorter treatment regimen (CDC 2013).

The effectiveness of INH in reducing the incidence of active TB (compared with placebo) is 60% to 90%. One study compared the efficacy of different durations of INH therapy: six months of treatment was 65% effective and 12 months was 75% effective (but not statistically different from six months) in preventing TB among patients with radiographic abnormalities suggestive of inactive infection (WHO 1982). Nevertheless, the efficacy of treatment is only about 60% (range 25% to 92%) due to the fact that not all patients complete the course of therapy (Smieja 2000, Jasmer et al. 2002).

The most important side effect of INH is hepatitis; the incidence is about 1 per 1 000 persons, although asymptomatic, mild liver-enzyme abnormalities are relatively common (Mitchell et al. 1976, Byrd et al. 1979, Nolan 1999).

Pyridoxine supplementation (25 to 50 mg daily) should be administered together with INH for patients with conditions that can predispose to neuropathy (including diabetes, uremia, alcoholism, malnutrition and HIV infection). It should also be administered to pregnant women and infants and to infants of breastfeeding mothers who are being treated with INH (American Thoracic Society 2000).

In light of concerns related to poor treatment adherence and adverse side effects, attempts have been made to develop alternative preventive TB treatments.

In 2011, the three-month regimen of INH and rifapentine (RPT) once weekly was recommended by CDC as an equal alternative to nine months of INH for treatment of LTBI in healthy patients years aged ≥12 (CDC 2003, Horsburgh and Rubin 2011).

Furthermore, a four-month daily dose of rifampin (RIF) (10 mg/kg with maximum dose of 600 mg) has been recommended. A four-month regimen of RIF can be considered for persons

who cannot tolerate INH or have been exposed to INH-resistant TB. The efficacy of RIF in reducing the incidence of active TB is estimated to be similar to that of INH (Hong Kong Chest Service/Tuberculosis Research Centre 1992, Villarino et al. 1997). Although data are limited, RIF appears to be well tolerated, with a low rate of hepatotoxicity (Hong Kong Chest Service/Tuberculosis Research Centre 1992).

In a study of 847 patients randomized to four months of RIF or nine months of INH, fewer adverse effects and better adherence were observed among those who received RIF, although the study did not evaluate efficacy (Menzies et al. 2008). Barriers to adoption of routine use of RIF for treatment of LTBI include the possibility of inadvertent treatment of active TB resulting in RIF-resistant disease, concerns about efficacy, and cost (Young et al. 2009, Aspler et al. 2010). Data on the use of INH and RIF in HIV-negative patients are limited (Ena and Valls 2005). For circumstances in which RPT is not available and/or directly observed therapy for INH-RPT is not feasible, a three-month daily regimen of INH-RIF may be an acceptable alternative.

Moreover, it has been documented that RIF with pyrazinamide is NOT recommended for treatment of LTBI due to the possibility of severe hepatotoxicity (2001, CDC 2003, McElroy et al. 2005, Ijaz et al. 2006). Ultimately, appropriate monitoring of side effects, as well as adherence, is crucial to LTBI treatment (Menzies 2011).

1.6 Adherence

According to the WHO report, adherence to long-term therapy is defined as “the extent to which a person’s behavior taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider”. Within the context of TB control, adherence is defined as “the extent to which the patient's history of therapeutic drug-taking coincides with the prescribed treatment” (WHO 2003). This differs from compliance as adherence assumes a patient’s understanding and agreement to follow medical advice. The literature attests to the fact that poor adherence to a prescribed treatment regimen is a common yet complex public health problem, which imposes a significant burden on the healthcare system and results in poor clinical outcomes (Brown and Bussell 2011, Iuga and

McGuire 2014). Indeed, treatment efficacy is often not achieved due to poor adherence as approximately 50% of patients do not follow their prescribed treatment regimen (Brown and Bussell 2011).

The advice and treatment healthcare providers deliver to patients and the patients' adherence to the regimen is of paramount importance to the outcome of an illness in multiple modalities; for example, prevention and progression of the disease, development of drug-resistant strains as a consequence of poor adherence to treatment resulting in high public healthcare costs. A 12-month course of LTBI treatment is 93% effective in adherent patients compared to 75% among the overall population (Comstock 1999). With this in mind, LTBI patients are to be considered a targeted population for targeted treatment as a modality for TB control strategy.

Patient education and understanding as to why drug therapy and adherence to the regimen are essential to prevent progression to TB and the consequential spread to one's own family and contacts. Effective communication with patients, the interpersonal relationship between clinicians, nurses and pharmacists working as a team are equally important to ensure effective adherence to treatment. Other factors that influence adherence are individual patient characteristics, socio-economic factors, infrastructure of the healthcare system and social support services (WHO 2003).

1.6.1 Factors influencing adherence

Various social determinants of health encompass individuals at birth, as they grow, live, work and age (WHO 2008). These determinants are influenced by external forces which include economic policies, social norms and political systems (IOM 2006). Ultimately, these social determinants form various layers within the context of a given individual and his environment and significantly impact all aspects of his health. This includes the individual's ability to access health care and adherence to recommended interventions when he does access health care. As per the WHO Commission on Social Determinants of Health, structural determinants of health are conditions that reinforce social stratification in society. As TB is a "social disease", social and structure determinants of health are particularly relevant to all aspects of TB control, including adherence to treatment. Within the context of TB, these include socioeconomic

inequalities, as well as high levels of population mobility and growth. As noted by Hargreaves et al. (2011), these structural determinants contribute to the unequal distribution of social determinants salient within the context of TB. Malnutrition, poor housing and environmental conditions, in addition to various financial, geographic and cultural barriers to healthcare access may be some key social determinants of adherence. Just as each of these determinants of health significantly impact exposure to infection, delayed diagnosis and treatment, they also impact adherence to treatment.

At the level of the patient, factors influencing adherence to treatment include not only age, race, gender, educational and socioeconomic status but also other associated variables including: knowledge about treatment regimen (Barnhoorn and Adriaanse 1992, Menzies et al. 1993), patients' perception of benefits of therapy and barriers to treatment (Janz and Becker 1984). It is not surprising that socio-economic factors, homelessness, psychiatric illnesses, lack of social support and stressful life events (Gordillo et al. 1999, Catz et al. 2000), specific cultural beliefs about drug therapy and disease transmission and progression (Bailey 1988, Rideout and Menzies 1994), have also been shown to impact adherence to treatment.

Healthcare provider characteristics and relationships impact on the patient's behavior. Quality of interpersonal skills and the physician's willingness and ability to explain and address the patient's concerns also influence adherence. The indifferent attitude of a treating physician and/or the failure to provide explanations for the need for treatment and the cause of illness have been shown to lead to non-adherence to treatment (Clark et al. 1998, Mead and Bower 2002). Regarding delivery of care, long waiting hours in clinics, inconvenient clinic hours and unaffordable travel costs have also been shown to negatively impact adherence (Orr et al. 1992, Besch 1995). In addition, treatment regimens that negatively impact adherence include multiple medications and dosing regimens, long duration of treatment and undesirable side effects as well as lifestyle changes such as dietary regimens (Eisen et al. 1990).

Also, disease characteristics such as minimal asymptomatic status affirming no need for treatment, minimal or no disability and the chronic versus acute nature of the illness that are all characteristics of LTBI may also influence adherence.

Children and adolescents have low adherence to treatment, the latter having less than

younger children, whose parental involvement may be the positive factor to adherence, whereas adolescents may be negatively influenced by peers and their social environment. As described so far, it becomes evident that a strategic approach is necessary to improve adherence and hence the CDC's "2010 healthy people objectives" target intended to include 85% of people diagnosed with LTBI to adhere to at least one course of treatment (CDC 2010).

1.6.2 Measures of adherence

Measures of adherence include both direct and indirect methods. As outlined by (Hirsch-Moverman et al. 2008) direct methods include directly observed preventive therapy, drug-level measurement and clinic attendance. Though DOPT has been documented in LTBI research (Lobato et al. 2005; White et al. 2003), it is not routinely used as a measure of adherence given that it is expensive and requires an extensive infrastructure and organization for maintenance. Drug-level measurement provides an objective measure of adherence (Hirsch-Moverman et al. 2008). While self-reported adherence to medication can be verified within the last 72 hours, this measure is expensive and inconvenient for the patient (Franks 2005). Many studies use clinic visits as a measure of adherence because they are cost effective. However, (Hirsch-Moverman et al. 2008) noted that although non-adherence is easily measured by this method, adherent clinic attendance does not necessarily reflect treatment adherence.

Indirect methods refer to patient self-reports, electronic monitoring devices (EDM), pill counts and prescription refill rates. Self-reports by way of detailed interviews are an efficient, cost-effective way to measure adherence and ascertain the reasons for defaulting (Hirsch-Moverman et al. 2008). Limitations include recall bias and false reporting, both of which may lead to an overestimation of treatment adherence (Hovell et al. 2003). Indeed, the authors reported that a composite of self-report measures and random urine assays provide an accurate estimate of INH adherence (Blumberg et al. 2005; Hovell et al. 2003). EDMs, such as the medication event monitoring system (MEMS), are considered accurate and objective measures of adherence (Hirsch-Moverman et al. 2008). The technology involves an electronic device, located in the cap of the pill container, which records the date and time when the bottle is opened (Menzies et al. 2005). Yet, limitations of the use of EDMs are that they are expensive, may be complex to use and they cannot account for the number of pills taken out that are ingested

(Franks 2005).

Indeed, Ailinger et al. reported that discrepancies between patient self-reports and MEMS data may indicate a possible limitation of MEMS (Ailinger et al. 2008). For instance, the authors explained that if numerous pills are taken out when the bottle is opened, then adherence as indicated by MEMS may be underestimated. Moreover, MEMS cannot prove dose ingestion such that patients may self-report taking more pills than MEMS recorded. Pill counts and medication refill rates are other forms of indirect measures of adherence that are cost effective yet are limited insomuch that they are unable to ensure pill ingestion (Franks 2005).

1.6.3 Strategies to improve adherence

Several factors have been identified as barriers to adherence. Beyond the scope of the treatment regimen itself and associated side effects, patient-related factors include co-existing medical conditions, limited financial resources, health beliefs and practices, cultural beliefs and real or perceived stigma related to treatment. As well, the relationship between the healthcare provider and the patient has been reported as a significant factor of adherence. Misinformation about the diagnosis and language barriers have been documented as deterrents to adherence.

Strategies that have been found to improve adherence to active as well as LTBI treatment include directly observed therapy (DOT) and case management (CDC 2011). While case management and DOT ensure patients' continuity of care, the latter provides close observation, which is particularly beneficial for high-risk patients. Furthermore, effective patient education has been found to promote adherence to treatment. Educational material available in patients' primary language and at the appropriate literacy level, heighten patients' understanding of their diagnosis and treatment regimen (Franks 2005). There is evidence that non-adherence in the first month of treatment is a good predictor of failure to complete treatment. Therefore, identifying non-adherent patients in the first month of treatment and taking corrective action may be a worthwhile strategy to improve adherence. As INH is the first line of treatment, the need for nine months of therapy, the potential for side effects and the need for follow up are common causes of failure. This randomized controlled trial by Menzies et al. shows that close monitoring and early adherence in the first four weeks are more likely to lead to the completion of treatment (Menzies et al. 2005).

Research conducted by Rennie et al. studied the effect of patient choice on completion of treatment and side effects (Rennie et al. 2007). Although the participants were not stratified according to age and ethnicity, the authors reported that when patients were given a three-month combination of INH and rifampin versus six months of INH treatment alone, 78% chose the shorter treatment regimen and demonstrated better adherence than those in the six-month treatment regimen. Though the efficacy and side effects of both treatment regimens were equal, given that adherence to treatment was higher for participants who chose the shorter treatment regimen, the authors suggest this modality should be strongly considered.

Chang et al. investigated whether house calls by community health workers and public health nurses had an effect on INH adherence and the frequency of side effects. 986 (25.2%) patients received house calls rather than clinic follow-ups. Though the factors associated with completion were not stratified and examined according to study criteria, the authors found that 90% of patients in the former group completed INH treatment versus 73% in the latter, adverse effects being similar, thereby suggesting that follow up of treatment in the form of house calls improves adherence to treatment (Chang et al. 2013).

In the study conducted by Ailinger et al., the authors examined Latino immigrants' knowledge of TB by way of an LTBI knowledge instrument questionnaire administered by the clinic. Patients scored a mean score of 66%, thereby indicating their need for further education regarding knowledge of the disease with respect to etiology, treatment, prevention and contagiousness. Though this article did not address factors associated with adherence to treatment, it emphasized the need for public health education of immigrants (Ailinger et al. 2004).

Anibarro et al. examined completion rates of LTBI treatment and risk factors associated with non-completion. Although the article did not stratify various factors associated with treatment completion, according to study criteria, the authors found that 80,8% of patients completed treatment while 19,2% did not. The risk factors associated with non-completion were unemployment, alcohol and drug abuse, residence in a correctional facility and recent immigrant status. Therefore, public health strategies should focus on correcting and improving these risk factors (Anibarro et al. 2010).

In the study conducted by Li et al., the authors examined completion rates of LTBI treatment and factors associated with adherence. They found that short duration of treatment and directly observed preventive treatment had a 20% higher completion rate. As well, the authors found that greater focus should be placed on contacts of TB and HIV patients (Li et al. 2010).

Similarly, Dobler & Marks (2013) examined completion rates of LTBI treatment and associated factors. In their population, preventive therapy was self-administered and dispensed monthly by the TB clinic. With primarily a foreign-born sample population, the study achieved a 75% completion. The authors found that patients' sex, age, country of birth, time since immigration, healthcare worker status, TST conversion status, chest x-ray findings, language, employment status and the indication for LTBI treatment were not significantly related to treatment completion. The authors noted that patient characteristics could not predict treatment completion.

Finally, cultural case management of LTBI was demonstrated as yet another effective strategy to improve adherence to treatment among refugees (Goldberg et al. 2004). The authors found that cultural case managers tailored to patients' ethnic background established a trusting relationship as they provided culturally appropriate TB education, as well as LTBI treatment and monitoring during monthly home visits where they addressed social service needs. Ultimately, this culturally sensitive intervention was effective as adherence to treatment was achieved among 82% of the foreign-born population.

Chapter 2: Article

TITLE PAGE

Adherence to latent tuberculosis treatment among immigrants in low endemic settings: a scoping review.

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2.1 Abstract

Background: Industrialized nations face an increase in TB due to immigration from TB-endemic nations. Particularly challenging is adherence to preventive treatment of latent TB infection (LTBI), which, when untreated, is associated with a 10% risk of developing active disease. The aim of this paper is to identify the determinants associated with adherence to LTBI treatment in the immigrant population residing in low TB-endemic countries.

Methods: A scoping review was performed using Medline, Medline in Process and Other Non-Indexed Citations, Embase, Global Health, Cumulative Index to Nursing and Allied Health Literature (CINAHL), as well as the Cochrane Library. Studies were limited to those published in English and French since 1997, involving adults, and conducted in immigrant-receiving counties with comparable socio-economic levels.

Results: In total, nine studies conducted in the United States were included in the analysis: two qualitative ethnographic, six quantitative observational and one quantitative interventional. Age, length of stay, sex, marital status, occupational status, country of origin, family support and drug-related side effects did not appear to be significant determinants of completion of preventive treatment. The factors that emerged as important for adherence and treatment completion were culturally- and linguistically-sensitive education about the disease and treatment objectives, selection of short treatment schedules, stable environment, and individualized care from dedicated healthcare providers.

Conclusions: Lack of adherence to prescribed treatment for LTBI by immigrants is a growing threat in low TB-endemic, immigrant-receiving countries. Our findings suggest that implementation of few low-cost provider-related factors can considerably improve the likelihood of treatment completion.

2.2 Background

Tuberculosis (TB), an infection caused by *Mycobacterium tuberculosis bacilli* (MTB) continues to be a major health problem worldwide. The 2010 World Health Organization (WHO) global burden of tuberculosis (TB) estimates that two billion people (about a third of the world's

population) are infected with MTB (WHO 2010). However, only 5% to 10% manifest clinically active TB disease (Lin and Flynn 2010). In the remainder of those infected, immune responses completely eradicate the infection in about 10%; in the remaining 90%, the immune response succeeds only in containment of the infection. In these individuals, the MTB evade the microbicidal mechanisms of immune cells and remain dormant and undetected, except by immunological tests, in granulomas in the lungs that are the immunological and physical barriers erected by the infected person's immune system to contain the infection (Reichman 2006, Gideon and Flynn 2011; Lin and Flynn 2010). This sub-clinical infection, with the potential for re-activation to develop active TB, is called latent TB infection (LTBI). As opposed to active TB disease, individuals with LTBI have no clinical or radiological signs of the tubercular disease and are diagnosed by a positive Tuberculin skin test reaction to purified protein derivative of MTB or a positive interferon-gamma release assay (IGRA) to MTB-specific antigens, although both tests are associated with false positive and false negative results in certain circumstances.

Although the MTB can remain inactive for several months, years or decades, individuals with LTBI have a risk of approximately 10% of developing active TB disease in their lifetime in the absence of a complete prophylactic treatment regimen (Schwartzman 2002; WHO 2009). Identification and treatment of LTBI greatly reduces the likelihood of reactivation and so has the potential to protect the health of infected individuals as well as the public by reducing the number of potential sources of infection (Horsburgh and Rubin 2011). With an ever-shifting global population, industrialized nations are experiencing a rising immigrant population originating from TB-endemic nations. Consequently, imported TB is found among this vulnerable population (Levesque et al. 2004, Story et al. 2006, Parsyan et al. 2007). The risk of reactivation TB is significant among immigrants with LTBI coming from countries with a high incidence of TB. More than half of all adults originating from TB-endemic countries have LTBI.

Treatment for LTBI is an essential component of TB control at large and low-incidence, immigrant-receiving nations have identified LTBI treatment as a vital component to prevent and, ultimately, eliminate TB (Menzies et al. 2005, Ailinger et al. 2006, Golub et al. 2006). Ultimately, appropriate monitoring of side effects, as well as adherence is imperative (Menzies 2011) in order to reduce the number of individuals who progress to active TB (Canadian Thoracic Society 2013). However, poor adherence to anti-tuberculous medications prevails as a

major obstacle to TB control, thereby increasing the risks of drug resistance, morbidity and mortality at both the individual and community levels (WHO 2003). In light of the heightened risk of reactivation among foreign-born men and women, adherence to LTBI treatment is one of the TB control strategies that has been underscored. Indeed, once a patient has completed screening and treatment has been initiated, adherence to therapy is a challenge of critical importance to TB control strategies. According to the WHO (WHO 2003), adherence is defined as "the extent to which a person's behavior (in this case, taking the prescribed treatment) corresponds with agreed recommendations from a healthcare provider." Several factors have been identified as barriers to adherence, including misinformation about the diagnosis, health beliefs and practices, medication side effects, language barriers and real or perceived stigma related to treatment (CDC 2011). Furthermore, the context of the immigrant is one that is unique and presents challenges different from those of the natives of a given country. According to a report published by the Robert Wood Johnson Foundation entitled "Living in America: Challenges facing new immigrants and refugees", some of these challenges include access to health care and social services, jobs, housing, language barriers and discrimination (Garrett 2006). Of relevance to the current topic of immigrants seeking help for treatment of TB, lack of legal status often discourages them from seeking medical care for fear of jeopardizing their immigration process. Moreover, language barriers pose a significant challenge, as immigrants are unable to effectively communicate with healthcare providers. Other challenges for immigrants noted by the authors include stigma surrounding their medical condition, long work hours and transportation problems, which often are found to hinder their use of healthcare services.

The asymptomatic nature of LTBI is in itself an issue to ensure adherence to a given treatment regimen. Unless healthcare providers understand contextual factors of immigrants that influence their adherence, they are unable to effectively address the inherent challenges. Recent appeals for further research and discussions relating to the complexities surrounding adherence to LTBI treatment regimens have brought to the forefront the necessity of defining key factors that are integral components of LTBI treatment completion.

2.2.1 Public health importance

Untreated/undertreated LTBI poses a significant threat not only to the infected individual

but also to the host community. The development of active TB in an individual with LTBI has far-reaching consequences (Holland et al. 2009). Pasipanodya and colleagues demonstrated significant respiratory impairment after the treatment of active TB, and the societal costs associated with this morbidity may be over $150,000 per case (Pasipanodya et al. 2007). Salpeter et al (Salpeter et al. 1997) estimated that even if only 20% of LTBI patients over 35 years of age received prophylaxis, more than 7000 deaths may be averted and healthcare expenditures reduced by more than $400 million. Supporting individuals with LTBI to adhere to prescribed treatments represents the last leg of an arduous (and expensive) journey that starts with the screening of high-risk immigrants, identification of infected individuals and initiation of treatment. Not seeing the preventive treatment through to completion means that the investment thus far is effectively wasted. As treatment for LTBI is only for a finite period, we feel that it is worthwhile to identify factors that could be implemented to improve adherence to treatment of LTBI.

2.3 Objective

The present review is aimed at identifying factors that have been found to improve adherence and completion of LTBI treatment in adult immigrants (18 years or older) in order to provide a framework for developing strategies to maximize adherence and completion of LTBI treatment in this vulnerable group.

2.4 Why a Scoping Review?

Our overarching aim was to identify, summarize and disseminate information about evidence-based interventions that improved adherence as well as to identify gaps that exist in the evidence base. We were not sure whether it was feasible or relevant to undertake a full systematic review as it was difficult to get a real sense of the extent, range and nature of research material/activity that might be available. Furthermore, we believed that, given the complex challenges faced by immigrants who require prolonged treatment for an asymptomatic condition, different study designs (rather than strictly quantitative studies) may be required to provide meaningful information about failure to complete the prescribed treatment.

2.5 Methods

2.5.1 General principles used to guide our review

We carried out our review with the same rigor and transparency that is required for systematic reviews (Mays and Pope 2000, Arksey and Malley 2005). As recommended by several experts on scoping reviews, we made our approach explicit and documented sufficient detail so as to enable the study to be replicated by others. Our primary intention was to identify all relevant literature, regardless of study design. Therefore, as would be expected, our process was not linear but iterative, requiring us to engage with each stage in a reflexive way. Where necessary, we repeated steps to ensure that the literature had been covered comprehensively.

We conducted the scoping review using the following steps adapted from the framework proposed by Levac et al. 2010 (Levac et al. 2010)

2.5.2 Stages of the review process

Stage 1: The research question
Stage 2: Identifying relevant studies
Stage 3: Study selection
Stage 4: Charting data
Stage 5: Collating, summarizing and reporting results

Table I

Framework Stages of scoping review*	Present scoping review study
1. The research question	Identifying determinants that influence adherence to LTBI treatment among foreign-born population residing in low TB-endemic, immigrant-receiving countries
2. Identifying relevant studies	• Medline, Medline in Process and Other Non-Indexed • Citations, Embase, Global Health, CINAHL and the Cochrane Library • Published in English and French • Database searches limited to studies published since 1997 • Keywords: tuberculosis, latent tuberculosis, inactive tuberculosis, emigration/immigration, refugees, emigrants/immigrants, ethnic groups, minority groups, ethnology, alien, minority, asylum-seeker, migration, foreign
3. Study selection	Inclusion criteria: • Studies conducted in Canada, the US, Europe, the United Kingdom, Australia and New Zealand • Adults over 18 years of age • All relevant and accessible quantitative and qualitative studies Exclusion criteria: • General reviews, commentaries, conference abstracts. • Aboriginal communities, healthcare workers, inmates, the homeless, injection drug users as well as patient populations with confounding co-morbidities such as HIV
4. Charting data	• Data extracted onto charting form (see Annexes I-IX) • Pilot test conducted prior to charting data
5. Collating, summarizing and reporting results	• Descriptive numerical summary – Tables 1 and 2 • Thematic analysis

* Framework criteria as postulated by Levac et al. Implementation Science, 2010

2.5.2.1 Stage 1: Identifying relevant studies

As the whole point of scoping a particular field is to be as comprehensive as possible in identifying primary studies and reviews suitable for answering the central research question, we searched for research evidence via different sources: Electronic databases: Medline, Medline in Process and Other Non-Indexed Citations, Embase, Global Health, Cumulative Index to Nursing and Allied Health Literature (CINAHL) as well as the Cochrane Library. Diverse keywords of the main concepts "latent tuberculosis infection" and "immigrant" were used until papers began to re-emerge. Keywords included tuberculosis, latent tuberculosis, inactive tuberculosis, emigration/immigration, emigrants/immigrants, refugees, ethnic groups, minority

groups, ethnology, alien, minority, asylum seeker, migration, and foreign. Despite the small risk of omitting a relevant study, as a conceptual rationale, the concept "immigrant" was used among the search terms as it is the focus of the study. As per the Canadian Council for Refugees, the concepts “immigrant”, “refugee”, and “asylum-seeker” were defined as:

immigrant	a person who has settled permanently in another country
refugee	a person who is forced to flee from persecution for reasons of race, religion, nationality, membership of a particular social group or political opinion
asylum seeker	a person who is seeking asylum

Though each foreign status is unique as to its challenges and access to health care, within the scope of this study, unless otherwise specified, these vulnerable populations will be referred to as immigrants. Furthermore, although adherence to LTBI treatment is the outcome being measured, given that it may not be the primary focus of a given study, the concept "adherence" was not included among the keywords to avoid overlooking any relevant articles. The database searches were limited to those published in English and French. We included only those studies published between 1997 and 2015, as this period marks the beginning of an increase in the proportion of TB cases among the foreign-born population in low-incidence countries including Australia, Canada, Norway, the Netherlands, US, UK, Israel, Switzerland, France and Germany (MacPherson and Gushulak 2006). Other language publications were excluded because of the cost and time involved in translating material. While we had to adopt these limits for practical reasons, we accept that we could have been missed potentially relevant articles.

2.5.2.2 Stage 2: Study selection inclusion/exclusion criteria

Studies were limited to those conducted in Canada, the US, Europe, the United Kingdom, Australia and New Zealand as these nations are considered developed, immigrant-receiving settings with similar socio-economic levels. We only included studies in which the populations in which we were interested (i.e., immigrants) were stratified or identified separately from other groups and factors affecting adherence in this specific population had been studied. The condition being treated had to be latent, not active TB. With regard to age, we focused on adults

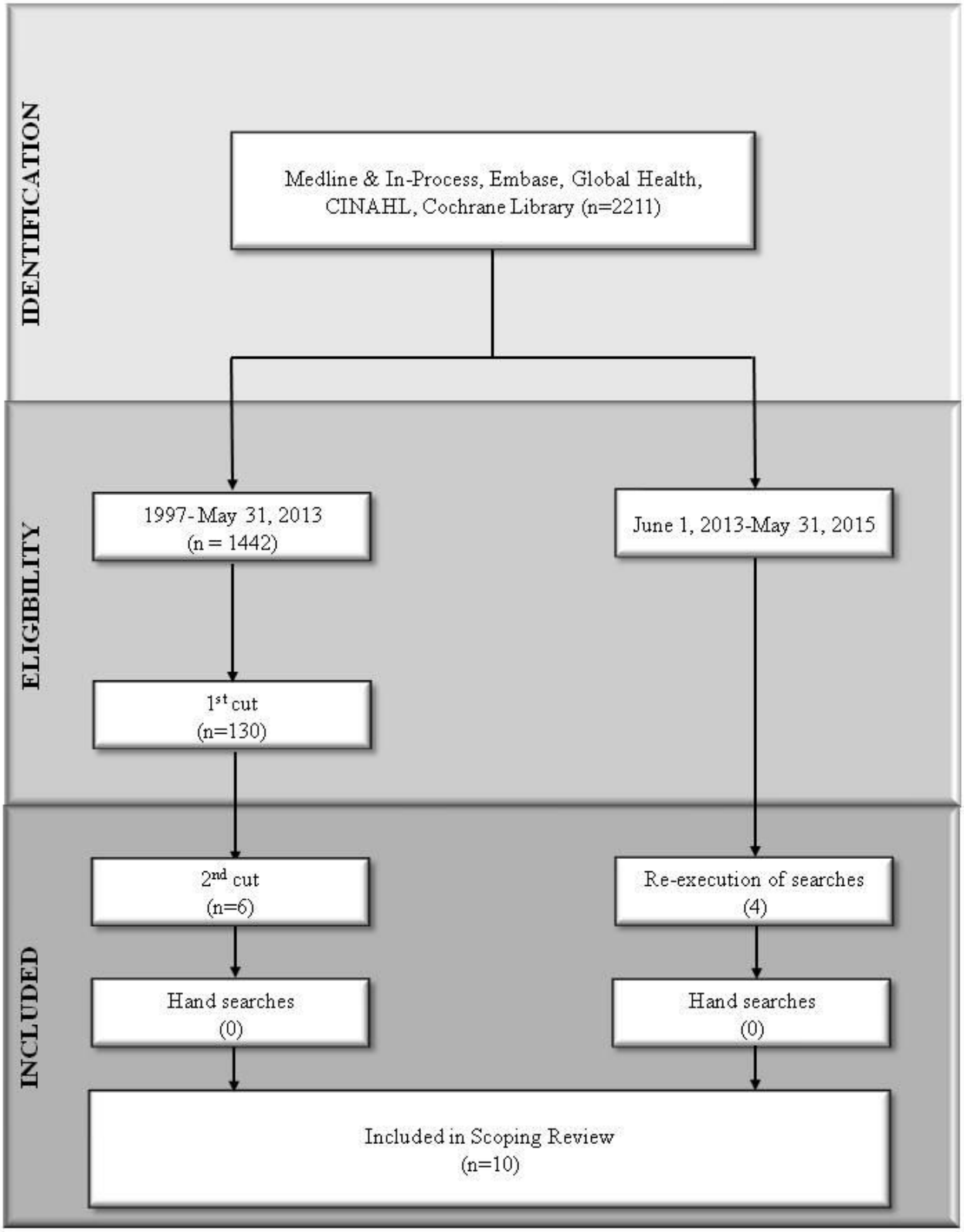
over 18 years. Children and adolescents were excluded in light of their greater susceptibility to develop TB and the unique tailored interventions required to meet the needs of this younger population. Severe forms of the disease occur at higher rates among young children in comparison to their older counterparts and hormonal changes, a heightened risk of reactivation and various psychosocial factors unique to adolescents, justify the importance of studying each group in their own right with respect to LTBI treatment (Morisky 2001, Coly and Morisky 2004, Stout et al. 2006, Finnell et al. 2009). Other vulnerable populations, including aboriginal communities, healthcare workers, inmates, the homeless, injection drug users, as well as patient populations with confounding co-morbidities such as HIV, were excluded despite their foreign status. Studies have demonstrated that each of these "at risk" populations face challenges unique to their specific population subgroup, thereby overshadowing the barriers that foreigners in general may encounter (Health Canada 2012; Malotte et al. 2001, Nyamathi et al. 2008, Lambert et al. 2012, White et al. 2012). All relevant and accessible quantitative and qualitative studies were included but general reviews, commentaries and conference abstracts were excluded from the analysis.

2.5.2.3 Stage 3. Data collection

A thesis log was maintained throughout the study in order to provide a detailed record of each step of the methodology and any issues that may have arisen.

Once the searches were conducted, all citations were exported to one EndNote library in order to keep track of included and excluded studies. A table was created to document the citation count throughout the study selection process (Figure 1).

Figure 1


IDENTIFICATION
Medline & In-Process, Embase, Global Health, CINAHL, Cochrane Library (n=2211)
ELIGIBILITY
1997- May 31, 2013 (n = 1442)
June 1, 2013-May 31, 2015
1st cut (n=130)
INCLUDED
2nd cut (n=6)
Re-execution of searches (4)
Hand searches (0)
Hand searches (0)
Included in Scoping Review (n=10)

The first cut of the study selection process entailed two reviewers independently screening/co-validating the title and/or abstract for relevance to adherence to LTBI treatment. As the citations were independently screened, if a given citation did not have an abstract in EndNote, the abstract (if available) was retrieved online and entered into EndNote (along with a separate URL link). If no abstract was available, yet the title seemed relevant to the study, it was included as a means of ensuring that no studies were overlooked. Three groups in EndNote "include", "exclude" and "to be determined", were created for the first cut, as a means of providing an effective way to keep track of excluded citations. Within a given excluded citation under the sub-heading "research notes", the reason for the exclusion was documented. Studies within the group "to be determined" represented those that required further discussion to assess their inclusion in the first cut of the study. Prior to the start of the data collection, the reserchers met to co-validate the EndNote library as well as to ensure that the inclusion and exclusion criteria were clear and concise prior to proceeding with the first cut of the co-validation process. They independently screened the title and abstract of each citation using EndNote and selected studies for potential inclusion in the scoping review. According to Levac et al. (2010), this study selection process minimizes the risk of subjectivity and of overlooking relevant studies. The researchers met regularly to compare notes. There were no disagreements about study selection/allocation.

The first cut of the study selection process was complete when the researchers confirmed that the "include" and "exclude" groups contained the exact citations and that all articles within the group "to be determined" had been reassigned.

Most articles were retrieved online or at the library (McGill or UofM). The two reviewers then independently reviewed each full-text study to ascertain its final inclusion in the study. The second cut required each reviewer to carefully examine details of the study, beyond the scope of the title and the abstract, as they pertained to the inclusion criteria. Indeed, the methodology and results section of each study were evaluated in depth to ascertain whether factors relating to adherence to LTBI treatment had been measured among the adult foreign-born population.

Once the final set of included studies had been confirmed, the data charting process began.

Copies of the full article were obtained for those studies that appeared to represent a "best

fit" with the research question. If the relevance of a study was unclear from the abstract, then the full article was acquired. Ultimately, nine articles were included in the scoping review.

2.5.2.4 Stage 4: Charting the data

The next stage of the work involved "charting" key items of information obtained from the primary research reports being reviewed. "Charting" (Ritchie and Spencer, 1994) describes a technique of synthesizing and interpreting qualitative data by sifting, charting and sorting material according to key issues and themes, a similar process to the one we adopted; hence we have borrowed the term. In a systematic review, this process would be called "data extraction."

Decisions had to be made about what information should be recorded from the primary studies. Simply producing a short summary or profile of each study does not guarantee helping those readers who might have to make important decisions based on the study findings (Pawson, 2002).

The data that we charted were entered onto a "data charting form." Generally speaking, this will be a mixture of general information about the study and specific information relating to, for instance, the study population, the type of intervention, outcome measures employed and the study design. The data charting forms for each of the nine studies can be found in Annexes I-IX.

As per Levac et al. (2010), the preliminary data charting form was developed with the primary research question in mind. A pilot test was then conducted with two studies prior to charting the data and issues were addressed regarding the extent of the data to be charted. Moreover, adjustments were made to the data charting form. Indeed, details were incorporated into the form following further reading and insight into relevant data needed for the analysis. The form was drafted in a Word document as a means to facilitate the data charting and analysis processes.

2.5.2.4.1 Hand search

A hand search was conducted among the bibliographies of all articles included in the final analysis, in order to demonstrate that every effort had been made to seek out relevant studies. Eventually, a saturation point was reached where no new studies were being identified, thus

ensuring the accuracy of the scoping review.

2.5.2.4 Stage 4: Collating, summarizing and reporting the results

Once the data were charted, two tables were created. Table I outlines the aim of each included study and the methodological design. The table provides an overview of the areas of research examined and relevant gaps. Table II provides further details of each study with respect to adherence to LTBI treatment among foreign-born participants.

2.6 Results and Discussion

2.6.1 Overview of the nine papers included in this review

Table II provides an overview of the objective and the study design of the articles included in the study.

Table II

Author(s) (Year)	Aim of the study	Design
Ailinger et al (1998)	To examine the influence of demographic factors, self-assessment of health, side effects and, support on adherence and medication during preventive treatment for LTBI	Descriptive survey
Ailinger et al (2006)	To examine the prevalence of adherence to LTBI therapy and the influence of basic conditions factors on the adherence among Latino immigrants	Exploratory Cross-Sectional
Ailinger et al (2007)	To examine the Predictors of Adherence to Latent Tuberculosis Infection Therapy in Latino Immigrants at a Public health clinic	Descriptive study
Ailinger et al (2010)	To report the Cultural Intervention and the adherence to LTBI treatment among subjects who receive the intervention compared with a historical/comparison sample	Pre-experimental designed
McEwen et al (2005)	To reveal how the multiple and disparate explanations of latent tuberculosis infection (LTBI) from the US and Mexican professional health sectors and the popular sector are used to inform the explanatory model (EM) of LTBI for Mexican immigrants residing in the U.S.-Mexico border region	Ethnographic study
McEwen et al (2007)	To explore how a group of Mexican immigrant women (N = 8) at risk of LTBI treatment failure interpreted and ultimately resisted LTBI preventive treatment	Critical ethnographic methodology
Bennett et al (2014)	To determine the prevalence and treatment rates of LTBI in newly arrived refugees and assess demographic and clinical characteristics associated with these outcomes	Descriptive / quantitative observational
Peluso et al (2014)	To evaluate LTBI program which provides LTBI treatment to an underserved, high-risk, foreign-born population	Retrospective chart review
Subedi et al (2015)	To compare the evaluation and treatment of LTBI in refugees seen at PRHC and non-PRHC clinics	Retrospective cohort study

Table III outlines the main characteristics of the nine studies included.

Table III

Study's author	Subjects	Measures of adherence	Treatment	Follow-up	Main findings
Ailinger et al (1998)	Latino Immigrants	Monthly appointments at the clinic and daily medication	6 months INH	6 months	No significant relationship between adherence and demographics, with exception of education. Adherence to clinic visits – Dropped from 81% at initial clinic appointment to 59% at the end of 6 months. Adherence to medication – Dropped from 89% at one month and 64% at 6 months.
Ailinger et al (2006)	Adult Latino Immigrant	Number of months patients had medication in chart reviews	9 months	8 months	Prevalence of LTBI adherence dropped from 98% at 2 months and to 72% at 9 months. Mean number of months adherent was 7.4 (SD=2.3). No significant relationship between adherence and demographics.
Ailinger et al (2007)	Latino Immigrant	Number of months that the client was present in a clinic appointment and reported taking the INH.	9 months	8 months	Adherence: mean number of months was 4.71 (range=0.8, SD=3.1) and dropped off in a linear fashion from month 1(84%) to month 8 (34%). 34% of the patients completed 8 months of LTBI therapy and were given their final month supply. No significant correlation between demographics and adherence to treatment were found. Only 2 factors were significantly related to adherence: the occurrence of side effects and the number of different PHNs who saw the client during treatment.
Ailinger et al (2010)	Latino Immigrants	Self-report of number of pills taken	9 months	9 months	Intervention was efficacious. Statistically significant difference between the 2 groups. The intervention group took a greater number of pills than the historical/comparison group and the difference was significant, t(85)=1.94, p=.028. Intervention group taking 28 doses (or almost a month's treatment) more than the historical group.
McEwen et al (2005)	Mexican immigrants in USA				For the Mexican Immigrants, understanding of LTBI was constructed in the context of multiple and conflicting explanations from the popular and professional sectors that are historically unique and foundational to the border region. The discrepancies between the explanations of LTBI from the US and Mexican professional health sectors contributed to suspicion and distrust of the diagnosis and resulted in participants questioning the veracity of health care providers on both sides of the border.

Study's author	Subjects	Measures of adherence	Treatment	Follow-up	Main findings
McEwen et al (2007)	Mexican Immigrants in USA				For participants, their interpretations and responses to LTBI treatment extend beyond the concept of treatment adherence. To contextualize the study findings the discussion situated within the perspective of oppression and resistance that is historically rooted in the US-Mexico border region. The study provides an account of how Mexican immigrant women avoided direct confrontation with health system but nevertheless, through everyday forms of resistance, managed to assert control over choices about their own health and welfare.
Bennett et al (2014)	refugees	Completion of treatment	INH		Of 373 refugees who initiated treatment, 219 (58.7%) completed LTBI treatment. In the bivariate analysis, refugees with 7- 12 years of education were significantly more likely to complete treatment than were refugees with 6 or fewer years of education.
Peluso et al (2014)	Foreign born population - (92%) central or south America	Number of months patients had medication as per medical record	9 months INH		• primary risk factor for LTBI was prior residence in TB endemic country (usually in last 5 years) • 26 (67%) patients had documented completion of 9 months of INH • median time-to-discontinuation was 273 days in group that completed treatment • those who completed treatment had less frequent encounters and phone encounters than the managed discontinuation and lost to follow-up groups, respectively
Subedi et al (2015)	Refugees with class B (non communicable) TB	Completion of treatment			• of the 57 (38.3%) patients with LTBI, 43 patients (75.4%) completed treatment • refugees seen at PRHC clinics more likely to complete treatment compared to those seen at non-PRHC clinics (OR 9.44, 95% CI 2.39-37.30)

Briefly, four of the studies included in this review are quantitative studies by Ailinger and colleagues, spanning from 1998 to 2010 (Ailinger and Dear 1998, Ailinger et al. 2006, Ailinger et al. 2007, Ailinger et al. 2010), which examined adherence to LTBI treatment by adult Latino immigrants in Washington DC, US. The researchers used Orem's Self-Care Deficit Theory to guide their exploratory research. This theory posits that adherence to preventive therapy is an indication of the individual's self-care based on deliberate action. Self-care practices in this context are those activities that an individual performs "in the interest of maintaining life" and "healthful functioning" (Orem 1995, Orem 2001). Self-care practices are influenced by self-care requisites and by "basic conditioning factors" such as gender, age, sociocultural factors,

environmental factors, health and developmental state, pattern of living, family system factors, healthcare system factors and availability of resources. In its first three studies published in 1998, 2006 and 2007, the Ailinger group studied the influence of these factors on adherence. The 1998 study focused on a convenience sample of 65 adult Latino immigrants attending a public clinic in Washington DC, US (study period not specified). The age of the participants ranged from 18 to 44 years, with a mean of 29. The aim of the study was to examine the influence of demographic factors, self-assessment of health, side effects and support, on adherence to appointments and medication taken during six months of INH treatment. In their 2006 study, Ailinger et al. conducted an exploratory cross-sectional study by examining the medical records of 53 adult Latino immigrants, with the aim of ascertaining the influence of basic conditioning factors on adherence to nine months of INH therapy. The age of participants ranged from 18 to 40 years, with a mean of 27,3. Average time in the US was six years, which ranged from 1 to 22 years. In 2007, Ailinger et al. published their descriptive study in which they had randomly examined selected medical records of 153 adult Latino immigrants treated at a public health clinic between 2004 and 2005 (clinic site not specified) in order to ascertain the predictors of adherence to nine months of INH treatment. The age of participants ranged from 18 to 56 years, with a mean of 26,1. The number of years in the US ranged from 1 to 22 years, with a mean of 4,58. In their fourth study, Ailinger et al. (Ailinger et al. 2010) studied the effect of a "cultural intervention" on improving adherence rates of a convenient sample of 53 adult Latino immigrants attending a public health clinic in Virginia. The interventional group (time period not specified) was compared to a historical group of 131 adult Latino immigrants with a similar demographic profile (time period not specified). The mean age of the interventional group was 25,49. Average time in the US was 3,83 years. The two studies by McEwen and colleagues that qualified for inclusion in this review (McEwen 2005, McEwen and Boyle 2007) are qualitative studies that explored how, and to what extent, an immigrant's explanatory model (EM) of illness influenced his/her adherence to therapy. For her 2005 publication, McEwen studied a convenience sample of 14 adult Mexican immigrants recruited from a TB clinic located in an American community in Arizona that borders the Mexican state of Sonora (study period not specified). The aim of the study was to identify how multiple and disparate explanations of LTBI from US and Mexican professional health sectors as well as the popular sector might inform the explanatory model of LTBI for Mexican immigrants residing in the US/Mexico border region. The age of participants

ranged from 25 to 72 years. In her 2007 publication, McEwen used multiple methods such as participant observation, a demographic questionnaire, participant interviews and review of medical records of eight adult Mexican immigrant women, aged from 19 to 40 years, recruited by TB clinical staff members to conduct a critical ethnographic study. Participants had resided in the US for a mean of 14,6 years. The study explored how this cohort, at risk of defaulting from the nine-month INH treatment regimen, interpreted and ultimately resisted LTBI treatment.

These qualitative studies were integral to this review, underscoring the importance of delving beyond the quantitative aspects of treatment adherence to understand the contextual factors surrounding adherence to LTBI treatment. The retrospective quantitative study published by Peluso et al. in 2014 aimed at evaluating the Latent Tuberculosis Initiative at the Haven Free Clinic, which provides nine months of INH treatment to an underserved, high-risk, foreign-born population in New Haven, Connecticut. The medical charts of 39 foreign-born patients, 92% originating from Central or South America, treated from January 2007 to December 2012, were reviewed. The age of patients ranged from 21 to 54 years, with a median of 34 years. The 2014 study conducted by Bennett et al. (Bennett et al. 2014) aimed at determining the prevalence and treatment rates of LTBI in newly-arrived refugees and assessing demographic and clinical characteristics associated with these outcomes. Refugees had been evaluated through the San Diego County Refugee Health Assessment Program (RHAP) from January 1, 2010, to October 1, 2012. Although the study included refugees aged 13 years and older, the authors stratified and analyzed adult refugees over 18 years of age separately. Lastly, the final retrospective cohort study published by Subedi et al. in 2015 aimed at comparing the evaluation and treatment of LTBI in refugees seen in Philadelphia Refugee Health Collaborative (PRHC) versus non-PRHC clinics from 2010 to 2012. Refugees were assigned to a PRHC clinic unless they chose to receive their health care at a non-PRHC clinic. The treatment was not specified, yet the authors noted that the PRHC clinic made an effort to complete preventive treatment before expiry of the refugees' temporary public insurance coverage, which was eight months post arrival.

2.6.2 Representativeness of men and women in the study population

Women were overrepresented in the Ailinger and McEwen studies, representing 80% of clients in the 1998 Ailinger study, 64% in her 2006 study, 63% in her 2007 study and 72% in her

2010 study.

Women formed 57% of the sample in the 2005 McEwen paper, and 100% of the sample in her 2007 paper.

The proportion of women in the other three papers was more representative of the index population (adult immigrants): 38% (Bennett 2014), 47,4% (Subedi 2015), 44% (Peluso 2014).

2.6.3 Tools used to measure adherence in the included studies

The studies included in this review used various methods to measure adherence. In the 1998 Ailinger paper, self-reported medication intake, as well as clinic attendance, were used to measure adherence. A data collection form and an adherence score were developed to document the data. With regards to the adherence score, each clinic appointment kept and each self-reported adherence to daily INH intake over the course of the six-month treatment regimen were conferred one point each, for a possible combined total adherence score of 12. Patients' medical records were reviewed to ascertain adherence. This scoring system was pilot tested on ten patients prior to its use in order to ensure accuracy of adherence assessments. In her 2006 and 2007 studies, Ailinger assessed medication adherence by the number of months that the patient was adherent, clinic attendance as documented by the researchers and response to a phone call and/or letter from the public-health nurse. In the 2010 Ailinger paper, adherence was measured by the number of INH doses reportedly taken by the patients, as documented in their medical record. Peluso et al. (Peluso et al. 2014) measured adherence to a nine-month course of INH treatment. Patient self-reports on the number of pills taken per month served as a measure of adherence. TB advocates measured adherence using a standardized, structured questionnaire assessing the number of pills that had been taken in the past month. In the 2014 study by Bennett et al., adherence was defined as completion of the prescribed treatment, which was daily INH for six to nine months. However, the authors did not specify how adherence was measured. Subedi et al. (Subedi et al. 2015) also defined adherence as treatment completion and did not elaborate on how adherence was measured.

2.6.4 Determinants of adherence and completion of LTBI treatments in immigrants

Given the complexity of subject under review; i.e., the population involved as well as the

disease process, its treatment and the interplay of the various factors under scrutiny, it is difficult to identify isolated factors as having strong and independent influence on adherence and treatment completion. Nevertheless, we were able to separate those factors that emerged as having a significant and consistent effect on promoting adherence and completion of treatment from those that appeared to have little or no influence and those that had inconsistent associations (in some studies and not others).

2.6.5 Factors that have minimal or no impact on adherence and completion

No significant correlation was seen between adherence/treatment completion and client-related variables such as age, country of birth, number of years since immigration, gender, age, languages spoken, family support and client perceived state of health in any of the studies included in this review.

2.6.6 Factors associated with adherence and completion of LTBI treatment in in some studies

2.6.6.1 Side effects

It would stand to reason that side effects would have a negative effect on adherence and completion of therapy, particularly for an asymptomatic condition. The top two contenders of the treatment of LBTI are nine months of INH or four months of Rifampicin. Both regimens are associated with minor side effects as well as the potential for major life-threatening hepatotoxicity. In the 1998 Ailinger study, in which nine months of INH was used, 40% of patients reported side effects. The most common were fatigue (29%), nausea (15%), tingling (15%), a rash (11%), loss of appetite (8%) and jaundice (8%). However, adherence was not significantly different between those who reported side effects and those who did not. In the 2006 Ailinger study, adverse reactions as a cause of discontinuation of therapy were documented in only 5,7%. In the Ailinger 2007 study, although 38% reported side effects, only 3% discontinued therapy and that too with medical advice. Only two factors were significantly related to adherence: the occurrence of side effects ($r=0,212$, $p=0,015$) and the number of different Public Health Nurses (PHN) who saw the client during treatment ($r=0,646, \leq 0,001$)p. However, on multi-varied analysis, only the number of PHN's remained significant.

Therefore, although side effects are cited as a cause of lack of adherence/discontinuation, the results of this scoping review as well as the wider literature suggest that although side effects contribute to low completion rates, they account for only a small fraction of the patients who discontinue treatment (Horsburgh and Rubin 2011). In carefully monitored patients without co-morbid conditions and who do not abuse of alcohol or use intravenous drugs, side effects are low and do not seem to be a significant factor for patient initiated drug discontinuation (Menzies et al. 2008).

However, *fear* of side effects emerges as a significant factor for non-adherence in individuals who are unsupervised/unsupported, do not have a close relationship with their healthcare providers or who do not understand the reasons for prophylactic treatment of their asymptomatic "disease" (McEwen and Boyle 2007). In her qualitative study, McEwen noted that the prescribed treatments were not even started or stopped prematurely due to fear of side effects. The participants provided "medical" reasons as to why they should not take the medication ("It irritated my stomach, so I stopped taking it." "My blood pressure scares me more right now than the TB does." "I did start taking it. But then, I had to stop because I have an ulcer, it will bother my stomach." "I did start the medicine, but then my doctor in Mexico said I had to take another medication for a kidney infection so I stopped it." [INH]) McEwen posits that women felt the need to "equalize power between themselves and their healthcare providers by exerting control over their LTBI treatment decisions using the provider's language." As this was a convenient sample of women only, we do not know if these findings apply also to men.

It is important to differentiate between the impact of actual side effects and the fear of side effects on non-adherence and discontinuation of LTBI treatment, as each warrant completely different approaches. With respect to fear of side effects and minor side effects, McEwen's recommendation that contextually meaningful information presented in a manner that reduces power imbalances between the provider and the client and engaging the client in an egalitarian approach, may go some way to helping immigrants make an informed decision about adhering to preventive treatment in the face of minor side effects.

2.6.7 Factors consistently found to have significant impact on adherence and completion of LTBI treatment in immigrant population

Certain factors emerged consistently across all the studies, qualitative and quantitative, as having a positive impact on improving adherence and completion of treatment in an immigrant population.

These will be discussed below.

2.6.7.1 Duration of treatment and adherence

Randomized trials have shown that INH treatment is highly effective in LTBI, with approximately 90% protection provided by a complete nine-month course of INH. However, an important determinant of the effectiveness of the treatment of LTBI is adherence to the regimen, and the likelihood of completion is poor with regimens that require long duration of treatment. Furthermore, because prolonged duration of treatment with INH increases the risk of hepatotoxicity, close monitoring of liver-function tests is required, which poses additional strain and cost on the client as well as the healthcare system. Ailinger found in her 1998 study that over the period of six months, adherence to clinic appointments dropped from 81% to 60% and adherence to medication declined from 89% to 65%. In the Ailinger 2006 study, the researchers found that the mean number of months that study subjects adhered to treatment was 7,4. Over the course of the study, adherence to treatment decreased from 98% at two months to 72% at nine months. However, the decrease in adherence rates was nonlinear, in that non-adherence was greater between four and seven months as compared to the last three months of the treatment regimen. In their 2007 study, Ailinger et al. reported a 47% adherence rate at six months, which decreased over the following two months to the point where only 34% of participants completed eight months of LTBI treatment. Ultimately, patients were adherent for a mean of 4,71 months (Ailinger et al. 2007). This finding is of importance as the second recommended regimen – administration of rifampicin – is needed only for four months. Rifampicin for four months has not been directly evaluated for effectiveness in a head-to-head trial with nine months of INH, but in one randomized trial, 60% protection was conferred by rifampin for three months (A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong (Hong Kong Chest Service/Tuberculosis Research Centre

1992). The completion rates reported with nine months of INH, six months of INH and four months of daily rifampin are 45% to 60%, 55% to 57%, and 69% to 78%, respectively (Jasmer et al. 2002, Menzies et al. 2004). Other studies on unselected populations also confirmed the importance of keeping the duration of preventive treatment as short as possible. An analysis conducted by Hirsch-Moverman et al. (Hirsch-Moverman et al. 2008) in the US and Canada found that reducing the duration of treatment from six or nine months of INH to four months of rifampicin was followed by an increase in the completion rate from less than 50% to 75% .

A pragmatic reason to choose a shorter treatment regimen is highlighted by one of the publications included in this review: Subedi and colleagues strove to complete all medical evaluations and treatment before the expiration of the immigrants' temporary public insurance coverage, which is effective only for a short period following their entry into the US. By using a short regime this group was able to achieve a 75% completion rate, which was significantly higher than those achieved outside of their program (OR 9,44; 95% CI 2,39-37,30; Subedi et al. 2005).

2.6.7.2 Provider-related characteristics that improve adherence to LTBI treatment in immigrants

Factors relating to healthcare providers, their sensitivity and responsiveness to the special needs of this population, emerged in all of the studies included in this review as significant promoters of adherence. Clear communication in a culturally meaningful and consistent way about the difference between active TB and latent TB, benefits of preventive treatment, treatment-related risks and the importance of surveillance significantly improved adherence and treatment completion rates. Participants in McEwen's study (2005) indicated that they did not initiate preventive treatment because "they [healthcare providers] didn't explain it." "They didn't tell you what medications you need and what treatment you needed and so since they didn't take it seriously, like they didn't explain it the way it should be explained, that leaves people thinking, well it is not that serious. Otherwise they would have talked to me about it now, instead of sending me somewhere [TB Clinic]." One participant received more detailed information from her doctor during a subsequent pregnancy and reflected, "If they would have explained it to me the first time, I would have come [for treatment] because I like taking care of myself." McEwen

(2007) went further to emphasize the need for healthcare providers to elicit patients' understanding of LTBI as a means of understanding each other's perspective and to avoid the subtle coercion sensed by the patients. "Some women did not openly express their concerns aloud. In these instances, healthcare providers did not elicit participants' understanding of LTBI; instead they transmitted their expert explanations exclusively within the US health professional perspective." "Providers and patient each had a different perspective of what the other was saying."

In the 2007 Ailinger et al. study in which patients were cared for by various public health nurses (PHN's), the authors observed that adherence was significantly and positively related to the number of PHN's caring for patients over the course of the treatment ($r=0{,}646$, $p \leq 0{,}001$). This suggests that continuity of care does not necessarily imply that the clients had to see the same PHN at each visit. Rather, it was the message being conveyed to the patients that was "consistent and clear" that ensured adherence to LTBI treatment.

An interventional study by Ailinger (2010) provided further evidence for the crucial role of delivering a culturally relevant, consistent message. The aim of this study was to determine whether there would be greater adherence to LTBI treatment in a group of clients who receive a culturally relevant intervention (CI) compared with clients who receive usual care. Clients saw the same interventionist nurse (who was fluent in Spanish) so that they could develop a relationship based on Latino values. Personal information of significance to the client, such as the names of family members (e.g., children, spouse), were recorded in the medical record and referred to in subsequent visits – *personalismo* (personal attention). At each monthly clinic visit, the nurse started the clinical encounter with an enquiry about the client's family, based on the Latino value of family ties *(familism)*. A familiar Latino proverb was stated by the interventionist nurse at each clinic visit: *"Es mejor prevenir que lamenter"*

("It is better to prevent than to lament"), which became the logo for the study and was used on stickers and small gifts (e.g., keyring flashlight) that were distributed to the subjects at random visits. Latino-adapted educational materials, which included pictures of Latino families, were given to clients. In addition, culturally appropriate nonverbal communication, such as touching the arm of Latina women or the back of the shoulder of men, was incorporated into the

interaction. The authors reported a statistically significant increase in adherence to LTBI treatment in the intervention arm. Despite the complexities surrounding culture, the intervention was able to effectively identify key components of Latino culture that ultimately resonated with patients and fostered trust in their healthcare provider. This significantly adherence to the prescribed preventive treatment regimen.

Another provider-related strategy that substantially improved adherence was the approach adopted by the Philadelphia Refugee Health Collaborative (PRHC's) formed in Philadelphia, PA, US, to provide comprehensive case management for refugees. The PRHC's mission is to provide newly arrived refugees comprehensive services that includes primary care and public health screening. They are typically led by physicians with special expertise in primary care for new immigrants, and the services are reimbursed by Medicaid, a public insurance program available to refugees during their first eight months in the US. Each clinic works with a health liaison from one of the three resettlement agencies to coordinate scheduling and medical case management.

The PRHC clinic model offers a multidisciplinary approach whereby doctors, nurses, social workers and case-workers from both the volunteer agencies and the PDPH manage the screening, evaluation and treatment follow-up of the refugees. They contact the refugees to remind them of their appointments, call pharmacies to refill medication prescriptions and offer bilingual services and a preset visit schedule. Refugees seen at PRHC clinics were significantly more likely than those seen in other settings to attend a follow-up appointment (OR 4.53, 95%CI 1.36–16.27), or complete treatment, (OR 9.44, 95%CI 2.39-37.30) compared to those seen at non-PRHC clinics.

The Peluso study (2014) provided impressive proof of the powerful influence of client-centered, culturally congruent support, and pragmatic assistance on improving adherence and completion of treatment. What was particularly impressive about this program was that a free student-led program could achieve remarkable results under such challenging circumstances. The treatment regime was nine months of INH, which is associated with lowest adherence and completion rate of any regime, the clients were mostly uninsured, undocumented, non-English speaking individuals with low socio-economic status and limited education. The components that

contributed to success are the same as those found in the other studies described above – improved communication through shared language, continuity of care, the one-on-one relationship between providers and patients, direct phone access, improving communication and education, availability of outreach clinic and appointment and prescription refill reminders. Patients' concerns and misconceptions were addressed, including misconceptions that LTBI is not a disease because it is asymptomatic, fears that treatment will prevent access to other clinic services, breach confidentiality or lead to legal troubles). Despite these challenges, this package of client-centered interventions improved adherence and completion of treatment from 19% to 67%. The authors estimated that targeted LTBI management in this population could prevent over 1,300 cases of active TB in the first five years following immigration.

2.7 Strengths and weaknesses

2.7.1 Strengths

Our decision to carry out a scoping review provided us access to investigations that used a range of designs, thus providing meaningful insight into this complex area that could not have been achieved by confining our investigation to quantitative studies. The search was comprehensive and meticulous and yielded results that could be incorporated into improving healthcare delivery for the vulnerable population.

2.7.2 Weaknesses

Only nine studies from a single country formed the body of this review, of which four were led by Ailinger and two by McEwen. Women were overrepresented in six of the nine studies, although they form a smaller proportion of the index population. This may limit the generalizability of the conclusions.

2.8 Summary and recommendations

By adopting a social determinant of health perspective, we were able to identify determinants that are unique to the migrant context and have a significant role in adherence to LTBI treatment among this specific high-risk population. A focus on the adult migrant

population allowed for a better understanding of migrants' unique context as they face various inequalities and challenges that impact their health.

Furthermore, the treatment of LTBI is generally considered cost effective and a crucial component of the strategy toward elimination of tuberculosis in low-incidence countries (Horsburgh and Rubin, 2011; Holland et al 2009; Bennett et al 2014). The most important factors implicated in improving adherence and treatment that emerged from this scoping review were consistent across all the studies. The most important determinants included:

- cultural and linguistic congruence
- considering the client's beliefs
- developing trust so that misconceptions and fears can be allayed
- providing direct phone access to clients
- improving outreach
- providing free access to health care
- providing phone-call, appointment and prescription refill reminders

In addition, student-led programs appear to be as effective as more expensive senior physician-led programs.

The identified factors are largely provider-dependent, and do not require highly experienced personnel. Our findings indicate that an effective intervention can be realized at limited cost with the adoption of a few easily implementable measures.

2.9 References

Ailinger, R. L., P. Black, N. Nguyen and H. Lasus (2007). "Predictors of Adherence to Latent Tuberculosis Infection Therapy in Latino Immigrants." Journal of Community Health Nursing **24**(3): 191 - 198.

Ailinger, R. L. and M. R. Dear (1998). "Adherence to tuberculosis preventive therapy among Latino immigrants." Public Health Nursing **15**(1): 19-24.

Ailinger, R. L., D. Martyn, H. Lasus and N. Lima Garcia (2010). "The Effect of a Cultural Intervention on Adherence to Latent Tuberculosis Infection Therapy in Latino Immigrants." Public Health Nursing **27**(2): 115-120.

Ailinger, R. L., D. Martyn, H. Lasus and N. Lima Garcia (2010). "The effect of a cultural intervention on adherence to latent tuberculosis infection therapy in Latino immigrants." Public Health Nurs **27**(2): 115-120.

Ailinger, R. L., J. B. Moore, N. Nguyen and H. Lasus (2006). "Adherence to Latent Tuberculosis Infection Therapy Among Latino Immigrants." Public Health Nursing **23**(4): 307-313.

Arksey, H. and L. Malley (2005). "Scoping studies: towards a methodological framework." International Journal of Social Research Methodology **8**(1): 19 - 32.

Bennett, R. J., S. Brodine, J. Waalen, K. Moser and T. C. Rodwell (2014). "Prevalence and treatment of latent tuberculosis infection among newly arrived refugees in San Diego County, January 2010-October 2012." Am J Public Health **104**(4): e95-e102.

Canadian Thoracic Society (2013). "Canadian Tuberculosis Standards, 7th Edition 2013."

CDC (2011). "Treatment of Latent Tuberculosis Infection: Maximizing Adherence." Fact Sheets: 1-2.

Coly, A. and D. Morisky (2004). "Predicting completion of treatment among foreign-born adolescents treated for latent tuberculosis infection in Los Angeles." International Journal of Tuberculosis & Lung Disease **8**(6): 703-710.

Finnell, S. M. E., J. C. Christenson and S. M. Downs (2009). "Latent Tuberculosis Infection in Children: A Call for Revised Treatment Guidelines." Pediatrics **123**(3): 816-822.

Garrett, K. E. (2006). "Living in America: Challenges Facing New Immigrants and Refugees."

Gideon, H. P. and J. L. Flynn (2011). "Latent tuberculosis: what the host "sees"?" Immunologic research **50**(2-3): 202-212.

Golub, J. E., S. Bur, W. A. Cronin, S. Gange, N. Baruch, G. W. Comstock and R. E. Chaisson (2006). "Delayed tuberculosis diagnosis and tuberculosis transmission." The International Journal of Tuberculosis and Lung Disease **10**: 24-30.

Health Canada (2012). "Epidemiology of Tuberculosis in First Nations Living On-Reserve in Canada, 2000-2008."

Hirsch-Moverman, Y., A. Daftary, J. Franks and P. W. Colson (2008). "Adherence to treatment for latent tuberculosis infection: systematic review of studies in the US and Canada." Int J Tuberc Lung Dis **12**(11): 1235-1254.

Holland, D. P., G. D. Sanders, C. D. Hamilton and J. E. Stout (2009). "Costs and Cost-effectiveness of Four Treatment Regimens for Latent Tuberculosis Infection." American Journal of Respiratory and Critical Care Medicine **179**(11): 1055-1060.

Hong Kong Chest Service/Tuberculosis Research Centre, M. B. M. R. C. (1992). "A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong." Am Rev Respir Dis **145**(1): 36-41.

Horsburgh, C. R., Jr. and E. J. Rubin (2011). "Clinical practice. Latent tuberculosis infection in the United States." N Engl J Med **364**(15): 1441-1448.

Jasmer, R. M., P. Nahid and P. C. Hopewell (2002). "Latent Tuberculosis Infection." New England Journal of Medicine **347**(23): 1860-1866.

Lambert, L. A. M. P. H., R. H. B. S. Pratt, L. R. R. N. P. Armstrong and M. B. M. S. N. M. P. H. F. N. P. Haddad (2012). "Tuberculosis among Healthcare Workers, United States, 1995–2007." Infection Control and Hospital Epidemiology **33**(11): 1126-1132.

Levac, D., H. Colquhoun and K. O'Brien (2010). "Scoping studies: advancing the methodology." Implementation Science **5**(1): 69.

Levesque, J. F., P. Dongier, P. Brassard and R. Allard (2004). "Acceptance of screening and completion of treatment for latent tuberculosis infection among refugee claimants in Canada." International Journal of Tuberculosis & Lung Disease **8**(6): 711-717.

Lin, P. L. and J. L. Flynn (2010). "Understanding latent tuberculosis: a moving target." J Immunol **185**(1): 15-22.

MacPherson, D. W. and B. D. Gushulak (2006). "Balancing prevention and screening among international migrants with tuberculosis: population mobility as the major epidemiological influence in low-incidence nations." Public Health **120**(8): 712-723.

Malotte, C. K., J. R. Hollingshead and M. Larro (2001). "Incentives vs outreach workers for latent tuberculosis treatment in drug users." American Journal of Preventive Medicine **20**(2): 103-107.

Mays, N. and C. Pope (2000). "Qualitative research in health care: Assessing quality in qualitative research." BMJ **320**(7226): 50-52.

McEwen, M. M. (2005). "Mexican Immigrants' Explanatory Model of Latent Tuberculosis Infection." J Transcult Nurs **16**(4): 347-355.

McEwen, M. M. and J. Boyle (2007). "Resistance, health, and latent tuberculosis infection: Mexican immigrants at the U.S.-Mexico border." Research & Theory for Nursing Practice **21**(3): 185-197.

Menzies, D., Al Jahdali, H., and Al Otaibi, B. (2011). "Recent developments in treatment of latent tuberculosis infection." Indian Journal of Medical Research **133**(3): 257-266.

Menzies, D., M.-J. Dion, B. Rabinovitch, S. Mannix, P. Brassard and K. Schwartzman (2004). "Treatment Completion and Costs of a Randomized Trial of Rifampin for 4 Months versus Isoniazid for 9 Months." American Journal of Respiratory and Critical Care Medicine **170**(4): 445-449.

Menzies, D., M. J. Dion, D. Francis, I. Parisien, I. Rocher, S. Mannix and K. Schwartzman

(2005). "In closely monitored patients, adherence in the first month predicts completion of therapy for latent tuberculosis infection."The International Journal of Tuberculosis and Lung Disease **9**: 1343-1348.

Menzies, D., R. Long, A. Trajman, M.-J. Dion, J. Yang, H. Al Jahdali, Z. Memish, K. Khan, M. Gardam, V. Hoeppner, A. Benedetti and K. Schwartzman (2008). "Adverse Events with 4 Months of Rifampin Therapy or 9 Months of Isoniazid Therapy for Latent Tuberculosis Infection." Annals of Internal Medicine **149**(10): 689-697.

Morisky, D., et al. (2001). "Behavioral Interventions for the Control of Tuberculosis Among Adolescents." Public Health Reports **116**: 568-574.

Nyamathi, A., P. Nahid, J. Berg, J. Burrage, A. Christiani, S. Aqtash, D. Morisky and B. Leake (2008). "Efficacy of Nurse Case-Managed Intervention for Latent Tuberculosis Among Homeless Subsamples." Nursing Research **57**(1): 33-39 10.1097/1001.NNR.0000280660.0000226879.0000280638.

Orem, D. (1995). Nursing concepts of practice. St. Louis, Mosby -Year Book.

Orem, D. E. (2001). "Response to: Lauder W. (2001)The utility of self-care theory as a theoretical basis for self-neglect. Journal of Advanced Nursing 34(4), 545-551." J Adv Nurs **34**(4): 552-553.

Parsyan, A. E., J. Saukkonen, M. A. Barry, S. Sharnprapai and C. R. Horsburgh Jr (2007). "Predictors of failure to complete treatment for latent tuberculosis infection." Journal of Infection **54**(3): 262-266.

Pasipanodya, J. G., T. L. Miller, M. Vecino, G. Munquia, S. Bae, G. Drewyer and S. E. Weis (2007). "Using the St. George respiratory questionnaire to ascertain health quality in persons with treated pulmonary tuberculosis." Chest **132**(5): 1591-1598.

Peluso, M. J., A. Hung, A. Lukasiewicz, H. Chang, J. Ramallo, M. Bartlett, G. Friedland and P. Ellis (2014). "Successful management of latent tuberculosis infection in an underserved community by a student-run free clinic." J Health Care Poor Underserved **25**(2): 837-862.

Reichman, L. B., Hershfield, E.S., and Raviglione, M.C., Ed. (2006). Tuberculosis: A Comprehensive, International Approach. New York, informa healthcare.

Salpeter, S. R., G. D. Sanders, E. E. Salpeter and D. K. Owens (1997). "Monitored isoniazid prophylaxis for low-risk tuberculin reactors older than 35 years of age: a risk-benefit and cost-effectiveness analysis." Ann Intern Med **127**(12): 1051-1061.

Schwartzman, K. (2002). "Latent tuberculosis infection: old problem, new priorities." Canadian Medical Association Journal **166**(6): 759-761.

Story, A., R. van Hest and A. Hayward (2006). "Tuberculosis and social exclusion." BMJ **333**(7558): 57-58.

Stout, J. E., T. Ostbye, E. B. Walter and C. D. Hamilton (2006). "Tuberculosis knowledge and attitudes among physicians who treat young children in North Carolina, USA." International Journal of Tuberculosis & Lung Disease **10**(7): 783-788.

Subedi, P., K. A. Drezner, M. C. Dogbey, E. C. Newbern, K. Yun, K. C. Scott, J. M. Garland, M. J. Altshuler and C. C. Johnson (2015). "Evaluation of latent tuberculous infection and

treatment completion for refugees in Philadelphia, PA, 2010-2012." Int J Tuberc Lung Dis **19**(5): 565-569.

White, M. C., R. W. Nelson, L. M. Kawamura, J. Grinsdale and J. Goldenson (2012). "Changes in characteristics of inmates with latent tuberculosis infection." Public Health **126**(9): 752-759.

WHO (2003). "Adherence to long-term therapies: evidence for action."

WHO (2009). "Tuberculosis facts 2009 update."

WHO (2010). "Global tuberculosis control: key findings from the December 2009 WHO report." Weekly epidemiological record **85**(9): 69-80.

Chapter 3: Conclusion

In the last four decades, the proportion of active TB cases in the Canadian-born non-aboriginal population has decreased dramatically, from 67,8% to 11,8%. On the other hand, during the same period, the proportion of TB among foreign-born individuals increased from 17,7% to 67,0%, because of the flow of immigrants from countries with endemic TB (Canadian Tuberculosis Standards, 7th Edition, available at www.phac-aspc.gc.ca). The vast majority of cases of TB in North America, as well as in other developed countries, are the result of reactivated LTBI, and nearly all these reactivated cases could have been prevented by a course of recommended treatment. Treatment of LTBI is thus important, not only to safeguard the future health of infected individuals, but also to reduce the subsequent human and financial toll on the host country. However, adhering to prolonged preventive treatment with drugs that may produce unpleasant side effects – and for a disease that has no symptoms – is difficult for most individuals. For immigrants who are already grappling with significant challenges, such as inadequate housing, financial hardship, difficulty accessing health care, and problems with communication and integration, adherence to treatment is a significant problem.

Our aim was to try to identify factors that significantly interfered with adherence, as well the interventions that were effective in promoting it. Because we suspected that some of the difficulties experienced by immigrants and measures that helped improve adherence would not be easily quantifiable, we opted for a scoping review.

We confined our search to the adult immigrant population and determinants of adherence to preventive treatment. We identified only nine papers – all from the US – that satisfied our criteria. Six were led by two investigators (four by Ailinger, and two by McEwen), and predominantly on women, thus limiting the generalizability of the findings. Nevertheless, the review yielded surprising and encouraging results. We started the review expecting to find that that the main determinants of poor adherence would be client/patient related and thus difficult to address. We were instead surprised to find that several provider-dependent interventions had a significantly positive impact on adherence and completion of treatment for LTBI. Clear communication between healthcare providers and the immigrant population emerged as a powerful promoter of adherence. The communication must be ethno-culturally sensitive and take

into consideration the knowledge, attitudes and beliefs of the client. Immigrants are much more likely to adhere to the prescribed treatment if they clearly understand the rationale for the treatment and the risks and benefits. There is strong evidence for the crucial role of delivering a culturally-sensitive and consistent message. It is important to avoid subtle or overt coercion. Healthcare providers need to be approachable, willing and available to address misconceptions and reassure patients, particularly because asymptomatic patients are being treated with drugs with potential side effects.

Many immigrants have limited means and find the process of settling in a new environment difficult and stressful. Access to free health care and pragmatic help from providers with respect to reminders for appointments and refilling of prescribed medication, help with transportation and availability of outreach clinics with extended hours had a significant effect on promoting adherence and completion of treatment.

It was encouraging to find that considerable success was achieved in promoting adherence and treatment completion by medical-student-led clinics (Peluso, 2014) suggesting that the above measures can be instituted without inordinate expense and the need for highly-skilled personnel.

Implementing the above measures is feasible and has the potential of having a substantial impact on the ability of host countries to control the rising prevalence of TB.

Bibliographie

(2001). "From the Centers for Disease Control and Prevention. Update: Fatal and severe liver injuries associated with Rifampin and Pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations--United States, 2001." Jama **286**(12): 1445-1446.

Ailinger, R. L., R. Armstrong, N. Nguyen and H. Lasus (2004). "Latino Immigrants' Knowledge of Tuberculosis." Public Health Nursing **21**(6): 519-523.

Ailinger, R. L., P. Black, N. Nguyen and H. Lasus (2007). "Predictors of Adherence to Latent Tuberculosis Infection Therapy in Latino Immigrants." Journal of Community Health Nursing **24**(3): 191 - 198.

Ailinger, R. L., P. L. Black and N. Lima-Garcia (2008). "Use of Electronic Monitoring in Clinical Nursing Research." Clinical Nursing Research **17**(2): 89-97.

Ailinger, R. L. and M. R. Dear (1998). "Adherence to tuberculosis preventive therapy among Latino immigrants." Public Health Nursing **15**(1): 19-24.

Ailinger, R. L., D. Martyn, H. Lasus and N. Lima Garcia (2010). "The effect of a cultural intervention on adherence to latent tuberculosis infection therapy in Latino immigrants." Public Health Nurs **27**(2): 115-120.

Ailinger, R. L., D. Martyn, H. Lasus and N. Lima Garcia (2010). "The Effect of a Cultural Intervention on Adherence to Latent Tuberculosis Infection Therapy in Latino Immigrants." Public Health Nursing **27**(2): 115-120.

Ailinger, R. L., J. B. Moore, N. Nguyen and H. Lasus (2006). "Adherence to Latent Tuberculosis Infection Therapy Among Latino Immigrants." Public Health Nursing **23**(4): 307-313.

Akolo, C., I. Adetifa, S. Shepperd, J. Volmink (2010). "Treatment of latent tuberculosis infection in HIV infected persons." Cochrane Database of Systematic Reviews 1(CD000171).

American Thoracic Society (2000). "Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society." MMWR Recomm Rep **49**(Rr-6): 1-51.

Anibarro, L., S. Casas, J. Paz-Esquete, L. Gonzalez, A. Pena, M. R. Guerra, D. Sande, Calvi, L. o, M. Santin, G. o. t. S. S. o. C. M. Mycobacteria Study Group and S. Infectious Diseases (2010). "Treatment completion in latent tuberculosis infection at specialist tuberculosis units in Spain." The International Journal of Tuberculosis and Lung Disease **14**(6): 701-707.

Arksey, H. and L. Malley (2005). "Scoping studies: towards a methodological framework." International Journal of Social Research Methodology **8**(1): 19 - 32.

Aspler, A., R. Long, A. Trajman, M.-J. Dion, K. Khan, K. Schwartzman and D. Menzies (2010). "Impact of treatment completion, intolerance and adverse events on health system costs in a randomised trial of 4 months rifampin or 9 months isoniazid for latent TB." Thorax **65**(7): 582-587.

Bailey, E. J. (1988). "An ethnomedical analysis of hypertension among Detroit Afro-Americans." J Natl Med Assoc **80**(10): 1105-1112.

Barnhoorn, F. and H. Adriaanse (1992). "In search of factors responsible for noncompliance

among tuberculosis patients in Wardha District, India." Soc Sci Med **34**(3): 291-306.

Baroux, N. and E. D'Ortenzio (2010). "[Tuberculosis in Reunion island: epidemiological characteristics of notified cases, 2000-2007]." Medecine et Maladies Infectieuses **40**(1): 12-17.

Bennett, R. J., S. Brodine, J. Waalen, K. Moser and T. C. Rodwell (2014). "Prevalence and treatment of latent tuberculosis infection among newly arrived refugees in San Diego County, January 2010-October 2012." Am J Public Health **104**(4): e95-e102.

Besch, C. L. (1995). "Compliance in clinical trials." Aids **9**(1): 1-10.

Bhugra, D. and M. A. Becker (2005). "Migration, cultural bereavement and cultural identity." World Psychiatry **4**(1): 18-24.

Blumberg, E. J., M. F. Hovell, N. J. Kelley, A. Y. Vera, C. L. Sipan and J. P. Berg (2005). "Self-report INH adherence measures were reliable and valid in Latino adolescents with latent tuberculosis infection." Journal of Clinical Epidemiology **58**(6): 645-648.

Brown, M. T. and J. K. Bussell (2011). "Medication adherence: WHO cares?" Mayo Clin Proc **86**(4): 304-314.

Byrd, R. B., B. R. Horn, D. A. Solomon and G. A. Griggs (1979). "Toxic effects of isoniazid in tuberculosis chemoprophylaxis. Role of biochemical monitoring in 1,000 patients." Jama **241**(12): 1239-1241.

Canadian Thoracic Society (2013). "Canadian Tuberculosis Standards, 7th Edition 2013."

Cangelosi, G. A., R. J. Freeman, K. N. Lewis, D. Livingston-Rosanoff, K. S. Shah, S. J. Milan and S. V. Goldberg (2004). "Evaluation of a high-throughput repetitive-sequence-based PCR system for DNA fingerprinting of Mycobacterium tuberculosis and Mycobacterium avium complex strains." Journal of Clinical Microbiology **42**(6): 2685-2693.

Catz, S. L., J. A. Kelly, L. M. Bogart, E. G. Benotsch and T. L. McAuliffe (2000). "Patterns, correlates, and barriers to medication adherence among persons prescribed new treatments for HIV disease." Health Psychol **19**(2): 124-133.

CDC Chapter 2: Transmission and Pathogenesis of Tuberculosis.

CDC (2003). "Update: Adverse Event Data and Revised American Thoracic Society/CDC Recommendations Against the Use of Rifampin and Pyrazinamide for Treatment of Latent Tuberculosis Infection—United States, 2003." Morbidity and Mortality Weekly Report **52**(31): 735-739.

CDC (2010). "Healthy People 2010 -Final Review."

CDC (2011). "Treatment of Latent Tuberculosis Infection: Maximizing Adherence." Fact Sheets: 1-2.

CDC. (2012, March 13, 2013). "Tuberculosis (TB)." Retrieved August 29, 2015, 2015, from http://www.cdc.gov/tb/topic/basics/.

CDC (2013). Core Curriculum on Tuberculosis: What the Clinician Should Know.

CDC (2013). Medication Adherence.

Chang, A., A. Polesky and G. Bhatia (2013). "House calls by community health workers and public health nurses to improve adherence to isoniazid monotherapy for latent tuberculosis infection: a retrospective study." BMC Public Health **13**(1): 894.

Clark, N. M., M. Gong, M. A. Schork, D. Evans, D. Roloff, M. Hurwitz, L. Maiman and R. B. Mellins (1998). "Impact of education for physicians on patient outcomes." Pediatrics **101**(5): 831-836.

Colson, P. W., J. Franks, R. Sondengam, Y. Hirsch-Moverman and W. El-Sadr (2010). "Tuberculosis knowledge, attitudes, and beliefs in foreign-born and US-born patients with latent tuberculosis infection." Journal of Immigrant & Minority Health **12**(6): 859-866.

Coly, A. and D. Morisky (2004). "Predicting completion of treatment among foreign-born adolescents treated for latent tuberculosis infection in Los Angeles." International Journal of Tuberculosis & Lung Disease **8**(6): 703-710.

Comstock, G. W. (1999). "How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? Counterpoint." The International Journal of Tuberculosis and Lung Disease **3**(10): 847-850.

Coreil, J., M. Lauzardo and M. Heurtelou (2004). "Cultural Feasibility Assessment of Tuberculosis Prevention Among Persons of Haitian Origin in South Florida." Journal of Immigrant Health **6**(2): 63-69.

Dobler, C. C. and G.B. Marks (2012). "Completion of treatment for latent tuberculosis infection with monthly drug dispensation directly through the tuberculosis clinic." PLoS One 7(11): e48900.

Eisen, S. A., D. K. Miller, R. S. Woodward, E. Spitznagel and T. R. Przybeck (1990). "The effect of prescribed daily dose frequency on patient medication compliance." Arch Intern Med **150**(9): 1881-1884.

Ena, J. and V. Valls (2005). "Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: a meta-analysis." Clin Infect Dis **40**(5): 670-676.

Finnell, S. M. E., J. C. Christenson and S. M. Downs (2009). "Latent Tuberculosis Infection in Children: A Call for Revised Treatment Guidelines." Pediatrics **123**(3): 816-822.

Franks, J., Hirsch-Moverman, Y., and Colson, P. (2005). "Adherence to Treatment for Latent Tuberculosis Infection: A Manual for Health Care Providers." 1-59.

Frothingham, R., J. E. Stout and C. D. Hamilton (2005). "Current issues in global tuberculosis control." International Journal of Infectious Diseases **9**(6): 297-311.

Garrett, K. E. (2006). "Living in America: Challenges Facing New Immigrants and Refugees."

Gideon, H. P. and J. L. Flynn (2011). "Latent tuberculosis: what the host "sees"?" Immunologic research **50**(2-3): 202-212.

Girardi, E., C. A. Sabin, A. d'Arminio Monforte, B. Hogg, A. N. Phillips, M. J. Gill, F. Dabis, P. Reiss, O. Kirk, E. Bernasconi, S. Grabar, A. Justice, S. Staszewski, G. Fatkenheuer, J. A. Sterne, Antiretroviral Therapy Cohort Collaboration (2005). "Incidence of Tuberculosis among HIV-infected patients receiving highly active antiretroviral therapy in Europe and North America." Clin Infect Dis 41(12): 1772-1782.

Goldberg, S. V., J. Wallace, J. C. Jackson, C. P. Chaulk, C. M. Nolan (2004). "Cultural case management of latent tuberculosis infection." International Journal of Tuberculosis and Lung Disease 8(1): 76-82.

Golub, J. E., S. Bur, W. A. Cronin, S. Gange, N. Baruch, G. W. Comstock and R. E. Chaisson

(2006). "Delayed tuberculosis diagnosis and tuberculosis transmission." The International Journal of Tuberculosis and Lung Disease **10**: 24-30.

Gordillo, V., J. del Amo, V. Soriano and J. Gonzalez-Lahoz (1999). "Sociodemographic and psychological variables influencing adherence to antiretroviral therapy." Aids **13**(13): 1763-1769.

Hargreaves, J. R., D. Boccia, C. A. Evans, M. Adato, M. Petticrew, and J. D. H. Porter (2011). "The Social Determinants of Tuberculosis: From Evidence to Action." Am J Public Health 101(4): 654-662.

Health Canada (2012). "Epidemiology of Tuberculosis in First Nations Living On-Reserve in Canada, 2000-2008."

Hirsch-Moverman, Y., A. Daftary, J. Franks and P. W. Colson (2008). "Adherence to treatment for latent tuberculosis infection: systematic review of studies in the US and Canada." Int J Tuberc Lung Dis **12**(11): 1235-1254.

Hirsch-Moverman, Y., A. Daftary, J. Franks and P. W. Colson (2008). "Adherence to treatment for latent tuberculosis infection: systematic review of studies in the US and Canada [Review article]." The International Journal of Tuberculosis and Lung Disease **12**(11): 1235-1254.

Holland, D. P., G. D. Sanders, C. D. Hamilton and J. E. Stout (2009). "Costs and Cost-effectiveness of Four Treatment Regimens for Latent Tuberculosis Infection." American Journal of Respiratory and Critical Care Medicine **179**(11): 1055-1060.

Hong Kong Chest Service/Tuberculosis Research Centre, M. B. M. R. C. (1992). "A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. ." Am Rev Respir Dis **145**(1): 36-41.

Horsburgh, C. R., Jr. and E. J. Rubin (2011). "Clinical practice. Latent tuberculosis infection in the United States." N Engl J Med **364**(15): 1441-1448.

Hovell, M. F., C. L. Sipan, E. J. Blumberg, C. R. Hofstetter, D. Slymen, L. Friedman, K. Moser, N. J. Kelley and A. Y. Vera (2003). "Increasing Latino Adolescents' Adherence to Treatment for Latent Tuberculosis Infection: A Controlled Trial." Am J Public Health **93**(11): 1871-1877.

Ijaz, K., J. A. Jereb, L. A. Lambert, W. A. Bower, P. R. Spradling, P. D. McElroy, M. F. Iademarco, T. R. Navin and K. G. Castro (2006). "Severe or fatal liver injury in 50 patients in the United States taking rifampin and pyrazinamide for latent tuberculosis infection." Clin Infect Dis **42**(3): 346-355.

International Organization for Migration (2006). "Migration: A Social Determinant of the Health of Migrants." http://www.migrant-health-europe.org/files/FINAL%20DRAFT%20-%20IOM%20SDH.pdf

Iuga, A. O. and M. J. McGuire (2014). "Adherence and health care costs." Risk Manag Healthc Policy **7**: 35-44.

Janz, N. K. and M. H. Becker (1984). "The Health Belief Model: a decade later." Health Educ Q **11**(1): 1-47.

Jasmer, R. M., P. Nahid and P. C. Hopewell (2002). "Latent Tuberculosis Infection." New England Journal of Medicine **347**(23): 1860-1866.

Lambert, L. A. M. P. H., R. H. B. S. Pratt, L. R. R. N. P. Armstrong and M. B. M. S. N. M. P. H. F. N. P. Haddad (2012). "Tuberculosis among Healthcare Workers, United States, 1995–2007." Infection Control and Hospital Epidemiology **33**(11): 1126-1132.

Levac, D., H. Colquhoun and K. O'Brien (2010). "Scoping studies: advancing the methodology." Implementation Science **5**(1): 69.

Levesque, J. F., P. Dongier, P. Brassard and R. Allard (2004). "Acceptance of screening and completion of treatment for latent tuberculosis infection among refugee claimants in Canada." International Journal of Tuberculosis & Lung Disease **8**(6): 711-717.

Li, J., S. S. Munsiff, T. Tarantino and M. Dorsinville (2010). "Adherence to treatment of latent tuberculosis infection in a clinical population in New York City." International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases **14**(4): e292-e297.

Lin, P. L. and J. L. Flynn (2010). "Understanding latent tuberculosis: a moving target." J Immunol **185**(1): 15-22.

Lobato, M. N., R. R. Reves, R. M. Jasmer, J. C. Grabau, N. N. Bock and N. Shang (2005). "Adverse Events and Treatment Completion for Latent Tuberculosis in Jail Inmates and Homeless Persons*." CHEST Journal **127**(4): 1296-1303.

LoBue, P. A. and K. S. Moser (2003). "Use of Isoniazid for Latent Tuberculosis Infection in a Public Health Clinic." Am. J. Respir. Crit. Care Med. **168**(4): 443-447.

MacPherson, D. W. and B. D. Gushulak (2006). "Balancing prevention and screening among international migrants with tuberculosis: population mobility as the major epidemiological influence in low-incidence nations." Public Health **120**(8): 712-723.

Malotte, C. K., J. R. Hollingshead and M. Larro (2001). "Incentives vs outreach workers for latent tuberculosis treatment in drug users." American Journal of Preventive Medicine **20**(2): 103-107.

Mays, N. and C. Pope (2000). "Qualitative research in health care: Assessing quality in qualitative research." BMJ **320**(7226): 50-52.

McCarthy, A. E., L. H. Weld, E. D. Barnett, H. So, C. Coyle, C. Greenaway, W. Stauffer, K. Leder, R. Lopez-Velez, P. Gautret, F. Castelli, N. Jenks, P. F. Walker, L. Loutan, M. Cetron and f. t. G. S. Network (2013). "Spectrum of Illness in International Migrants Seen at GeoSentinel Clinics in 1997–2009, Part 2: Migrants Resettled Internationally and Evaluated for Specific Health Concerns." Clinical Infectious Diseases **56**(7): 925-933.

McElroy, P. D., K. Ijaz, L. A. Lambert, J. A. Jereb, M. F. Iademarco, K. G. Castro and T. R. Navin (2005). "National survey to measure rates of liver injury, hospitalization, and death associated with rifampin and pyrazinamide for latent tuberculosis infection." Clin Infect Dis **41**(8): 1125-1133.

McEwen, M. M. (2005). "Mexican Immigrants' Explanatory Model of Latent Tuberculosis Infection." J Transcult Nurs **16**(4): 347-355.

McEwen, M. M. and J. Boyle (2007). "Resistance, health, and latent tuberculosis infection: Mexican immigrants at the U.S.-Mexico border." Research & Theory for Nursing Practice **21**(3): 185-197.

Mead, N. and P. Bower (2002). "Patient-centred consultations and outcomes in primary care: a review of the literature." Patient Educ Couns **48**(1): 51-61.

Menzies, D., Al Jahdali, H., and Al Otaibi, B. (2011). "Recent developments in treatment of latent tuberculosis infection." Indian Journal of Medical Research **133**(3): 257-266.

Menzies, D., M.-J. Dion, B. Rabinovitch, S. Mannix, P. Brassard and K. Schwartzman (2004). "Treatment Completion and Costs of a Randomized Trial of Rifampin for 4 Months versus Isoniazid for 9 Months." American Journal of Respiratory and Critical Care Medicine **170**(4): 445-449.

Menzies, D., M. J. Dion, D. Francis, I. Parisien, I. Rocher, S. Mannix and K. Schwartzman (2005). "In closely monitored patients, adherence in the first month predicts completion of therapy for latent tuberculosis infection." The International Journal of Tuberculosis and Lung Disease **9**: 1343-1348.

Menzies, D., R. Long, A. Trajman, M.-J. Dion, J. Yang, H. Al Jahdali, Z. Memish, K. Khan, M. Gardam, V. Hoeppner, A. Benedetti and K. Schwartzman (2008). "Adverse Events with 4 Months of Rifampin Therapy or 9 Months of Isoniazid Therapy for Latent Tuberculosis Infection." Annals of Internal Medicine **149**(10): 689-697.

Menzies, R., I. Rocher and B. Vissandjee (1993). "Factors associated with compliance in treatment of tuberculosis." Tubercle and Lung Disease **74**(1): 32-37.

Mitchell, J. R., H. J. Zimmerman, K. G. Ishak, U. P. Thorgeirsson, J. A. Timbrell, W. R. Snodgrass and S. D. Nelson (1976). "Isoniazid liver injury: clinical spectrum, pathology, and probable pathogenesis." Ann Intern Med **84**(2): 181-192.

Morisky, D., et al. (2001). "Behavioral Interventions for the Control of Tuberculosis Among Adolescents." Public Health Reports **116**: 568-574.

Nolan, C. M., Goldberg, S.V., and Buskin, S.E. (1999). "Hepatotoxicity Associated with Isoniazid Preventive Therapy." JAMA **281**(11): 1014-1018.

Nyamathi, A., P. Nahid, J. Berg, J. Burrage, A. Christiani, S. Aqtash, D. Morisky and B. Leake (2008). "Efficacy of Nurse Case-Managed Intervention for Latent Tuberculosis Among Homeless Subsamples." Nursing Research **57**(1): 33-39 10.1097/1001.NNR.0000280660.0000226879.0000280638.

Orem, D. (1995). Nursing concepts of practice. St. Louis, Mosby -Year Book.

Orem, D. E. (2001). "Response to: Lauder W.(2001)The utility of self-care theory as a theoretical basis for self-neglect. Journal of Advanced Nursing 34(4), 545-551." J Adv Nurs **34**(4): 552-553.

Orr, P. R., D. W. Blackhurst and B. S. Hawkins (1992). "Patient and clinic factors predictive of missed visits and inactive status in a multicenter clinical trial. The Macular Photocoagulation Study Group." Control Clin Trials **13**(1): 40-49.

Pareek, M., I. Baussano, I. Abubakar, C. Dye and A. Lalvani (2012). "Evaluation of immigrant tuberculosis screening in industrialized countries." Emerging Infectious Diseases **18**(9): 1422-1429.

Parsyan, A. E., J. Saukkonen, M. A. Barry, S. Sharnprapai and C. R. Horsburgh Jr (2007). "Predictors of failure to complete treatment for latent tuberculosis infection." Journal of Infection **54**(3): 262-266.

Pasipanodya, J. G., T. L. Miller, M. Vecino, G. Munquia, S. Bae, G. Drewyer and S. E. Weis (2007). "Using the St. George respiratory questionnaire to ascertain health quality in persons with treated pulmonary tuberculosis." Chest **132**(5): 1591-1598.

Pawson, R. (2002). "Evidence-based Policy: In Search of a Method." Evaluation **8**(2): 157-181.

Peluso, M. J., A. Hung, A. Lukasiewicz, H. Chang, J. Ramallo, M. Bartlett, G. Friedland and P. Ellis (2014). "Successful management of latent tuberculosis infection in an underserved community by a student-run free clinic." J Health Care Poor Underserved **25**(2): 837-862.

Piggott, D. A. and P. C. Karakousis (2011). "Timing of Antiretroviral Therapy for HIV in the Setting of TB Treatment." Clinical and Developmental Immunology 2011: 10.1155/2011/103917.

Platform for International Cooperation on Undocumented Migrants (2007). "Access to Health Care for Undocumented Migrants in Europe." http://picum.org/picum.org/uploads/file_/Access_to_Health_Care_for_Undocumented_Migrants.pdf.

Public Health Agency of Canada (2012). Tuberculosis in Canada 2012.

Reichman, L. B., Hershfield, E.S., and Raviglione, M.C., Ed. (2006). Tuberculosis: A Comprehensive, International Approach. New York, informa healthcare.

Rennie, T. W., G. H. Bothamley, D. Engova and I. P. Bates (2007). "Patient choice promotes adherence in preventive treatment for latent tuberculosis." European Respiratory Journal **30**(4): 728-735.

Rideout, M. and R. Menzies (1994). "Factors affecting compliance with preventive treatment for tuberculosis at Mistassini Lake, Quebec, Canada." Clin Invest Med **17**(1): 31-36.

Ritchie, J. a. S., L (1994). Qualitative data analysis for applied policy research. Analyzing qualitative data. A. B. a. R. G. Burgess**:** 173-194.

Rivest, P., L. Sinyavskaya, P. Brassard (2014)."Burden of HIV and tuberculosis co-infection in Montreal, Quebec." Can J Public Health 105(4): e263-e267.

Rustad, T. R., A. M. Sherrid, K. J. Minch and D. R. Sherman (2009). "Hypoxia: a window into Mycobacterium tuberculosis latency." Cell Microbiol **11**(8): 1151-1159.

Salpeter, S. R., G. D. Sanders, E. E. Salpeter and D. K. Owens (1997). "Monitored isoniazid prophylaxis for low-risk tuberculin reactors older than 35 years of age: a risk-benefit and cost-effectiveness analysis." Ann Intern Med **127**(12): 1051-1061.

Schwartzman, K. (2002). "Latent tuberculosis infection: old problem, new priorities." Canadian Medical Association Journal **166**(6): 759-761.

Smieja, M. J., Marchetti, C.A., Cook, D.J., and Smaill, F.M. (2000). "Isoniazid for preventing tuberculosis in non-HIV infected persons." Cochrane Database of Systematic Reviews **2**(CD001363).

Story, A., R. van Hest and A. Hayward (2006). "Tuberculosis and social exclusion." BMJ **333**(7558): 57-58.

Stout, J. E., T. Ostbye, E. B. Walter and C. D. Hamilton (2006). "Tuberculosis knowledge and attitudes among physicians who treat young children in North Carolina, USA." International Journal of Tuberculosis & Lung Disease **10**(7): 783-788.

Subedi, P., K. A. Drezner, M. C. Dogbey, E. C. Newbern, K. Yun, K. C. Scott, J. M. Garland, M. J. Altshuler and C. C. Johnson (2015). "Evaluation of latent tuberculous infection and treatment completion for refugees in Philadelphia, PA, 2010-2012." Int J Tuberc Lung Dis **19**(5): 565-569.

Villarino, M. E., R. Ridzon, P. C. Weismuller, M. Elcock, R. M. Maxwell, J. Meador, P. J. Smith, M. L. Carson and L. J. Geiter (1997). "Rifampin preventive therapy for tuberculosis infection: experience with 157 adolescents." Am J Respir Crit Care Med **155**(5): 1735-1738.

White, M. C., E. Gournis, M. Kawamura, E. Menendez and J. P. Tulsky (2003). "Effect of directly observed preventive therapy for latent tuberculosis infection in San Francisco." International Journal of Tuberculosis & Lung Disease **7**(1): 30-35.

White, M. C., R. W. Nelson, L. M. Kawamura, J. Grinsdale and J. Goldenson (2012). "Changes in characteristics of inmates with latent tuberculosis infection." Public Health **126**(9): 752-759.

WHO (1948). "Constitution of the World Health Organization." http://www.who.int/governance/eb/who_ constitution_en.pdf.

WHO (1982). "Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial." Bulletin of the World Health Organization **60**(4): 555-564.

WHO (2003). "Adherence to long-term therapies: evidence for action."

WHO (2008). Overcoming migrants' barriers to health. Bulletin of the World Health Organization.

WHO (2008). "Closing the gap in a generation: health equity through action on the social determinants of health. Final Report of the Commission on Social Determinants of Health." http://www.who.int/social_determinants/thecommission/finalreport/en/.

WHO (2009). "Tuberculosis facts 2009 update."

WHO (2010). "Global tuberculosis control: key findings from the December 2009 WHO report." Weekly epidemiological record **85**(9): 69-80.

WHO (2013). Global Tuberculosis Report 2013.

Young, H., M. Wessolossky, J. Ellis, M. Kaminski and J. S. Daly (2009). "A retrospective evaluation of completion rates, total cost, and adverse effects for treatment of latent tuberculosis infection in a public health clinic in central Massachusetts." Clin Infect Dis **49**(3): 424-427.

ANNEX I

Data Charting Form				
Study reference				
Primary Author	Rita L. Ailinger			
Publication year	1998			
Title	Adherence to tuberculosis Preventive Therapy Among Latino Immigrants			
Journal	Public Health Nursing			
Volume	15			
Issue	1			
Pages	19-24			
Note(s)				
Study characteristics				
Study setting	City/Country	Study centre	%foreign born / %study population at risk	Year
	USA	County Health Dept, metropolitan Washington DC	100% foreign born 100% at risk population	Not specified
Theoretical model	Orem's Self-Care Deficit Theory			
Study design	Descriptive survey			
Data collection	Medical records reviews and personal interviews			
Recruitment method	Convenience sample of 65			
Population characteristics	Target population	Sample size		
	Latino Immigrants	65		
Demographics				
Age	Mean	Range	Categories	
	29.02	18-44	Not specified	
Sex	Female 52 (80%) and Male 13 (20%)			
Country of origin	El Salvador 63% Guatemala 9% Honduras 6% Nicaragua 5% Bolivia 6% Other 6%			
Visa status group	Immigrants			
Years in 'x' country	Not specified			
Race/ Ethnicity	Not specified			
Education	Average 8.50 Range 0-16 SD 3.74			
Marital status	Not Specified			
Occupation	Blue collar or on unskilled jobs			
Socioeconomic status	Not specified			
Religion	Not specified			
Language(s)	Not specified			
Other				
Aim of the study	Examine the influence of demographic factors, self-assessment of health, side effects and, support on adherence and medication during preventive treatment for LTBI.			
Outcome(s) measured	Adherence to treatment and influence of demographic factors, self-assessment of health, side effects and support.			
Focus of intervention	Not Applicable			
Number of conditions (including control)	Not Applicable			
Duration of intervention	Not Applicable			
Delivery mode of intervention	Not Applicable			
Primary staff	Not Applicable			
Training provided by	Not Applicable			

Latent TB treatment	Type of medication		Dose	Duration
	Isoniazid		Not specified	6 months
Follow-up	Type	Frequency	Duration	Carried out by
	Clinic visits	monthly	6 months	nurse
Adherence to LTBI treatment				
Definition	Self-care action of taking daily medication and keeping monthly clinic appointments			
Measure of adherence	Keeping monthly appointments at the clinic and taking daily medication			
Measurement tool	Data collection form and an adherence score			
Tool validated? If so, how?	Yes – pilot test with 10 clients			
Measurement carried out by	Clinic nurse			
Main findings	• Adherence to clinic visits – 81% of patients kept their initial clinic appointment and only 60% continued to keep the appointment at the end of 6 months • Adherence to medication – Dropped from 89% at one month and 65% at 6 months. • No significant difference in adherence to clinic attendance by gender, age or education. • Education was significantly correlated to medication adherence (r= 0.307, p=0.034). • No significant difference in adherence and reported support • No significant difference in adherence between those who reported side effects versus those who did not • No significant difference in adherence between those who reported excellent/good health versus those who reported fair/ poor health			
Limitations	Not specified			

ANNEX II

Data Charting Form				
Study reference				
Primary Author	Rita L. Ailinger			
Publication year	2006			
Title	Adherence to latent tuberculosis infection therapy among latino immigrants			
Journal	Public Health Nursing			
Volume	23			
Issue	4			
Pages	307-313			
Note(s)				
Study characteristics				
Study setting	City/Country	Study centre	%foreign born / %study population at risk	Year
	USA	Public Health Clinic in the Metropolitan Washington D.C area	100 / 100	Not Specified
Theoretical model	Orem's Self-Care Deficit Theory			
Study design	Exploratory Cross-Sectional			
Data collection	From Medical Records			
Recruitment method	All clients who met the eligibility criteria at a public health clinic in the metropolitan Washington DC area.			
Population characteristics	Target population	Sample size		
	Adult Latino Immigrant	53		
Demographics				
Age	Mean	Range	Categories	
	27.3	18-40	Not Specified	
Sex	64 % were female			
Country of origin	Mexico 5.7%, Guatemala 17%, Honduras 5.7%, El Salvador 26.4%, Colombia 1.9%,			
Visa status group	Not specified			
Years in 'x' country	Average time in USA – 6 years ; range 1-22			
Race/ Ethnicity	Not specified			
Education	Mean 10.54 years; range 1-22			
Marital status	Not specified			
Occupation	7.5 % were in skilled occupation; 7.5 % were unemployed; and the rest were in unskilled jobs such as restaurant work or construction			
Socioeconomic status	Not specified			
Religion	Not specified			
Language(s)	Not specified			
Other				
Aim of the study	Examine the prevalence of adherence to LTBI therapy and the influence of basic conditions factors on the adherence among Latino immigrants			
Outcome(s) measured	Adherence			
Focus of intervention	Not Applicable			
Number of conditions (including control)	Not Applicable			
Duration of intervention	Not Applicable			
Delivery mode of intervention	Not Applicable			
Primary staff	Not Applicable			
Training provided by	Not Applicable			

Latent TB treatment	Type of medication	Dose	Duration	
	ISONIAZID	Not specified	9 months	
Follow-up	Type	Frequency	Duration	Carried out by
	Clinic Visit	Monthly	8 months	Nurse
Adherence to LTBI treatment				
Definition	Adherence defined by number of months the client complete therapy (9 months of treatment). Not the number of dose medications			
Measure of adherence	Number of months patients had medication in chart reviews			
Measurement tool	Not specified			
Tool validated? If so, how?	Not specified			
Measurement carried out by	Not Specified			
Main findings	• Prevalence of LTBI adherence dropped from 98% at 2 months and to 72% at 9 months. • Mean number of months adherent was 7.4 (SD= 2.3) • No significant difference in adherence by gender, country of origin, languages spoken. • No significant correlations between total number of adherence and age, years of education, and number of years in the US. • There was a difference in the number of months adherent between those who knew someone who had TB (6 months adherence) versus those who did not (mean adherence of 8 months). • Non adherence due to adverse reactions in 3 cases (5.7%) • Other reasons for non-adherence- "refused services"- 9.4% and "moved" (3.8%)			
Limitations	Small sample size, lack of socioeconomic data, information about HIV status of sample members and not including the number of doses of INH in the analysis. Study did not assess barriers to completion of therapy.			

ANNEX III

Data Charting Form				
Study reference				
Primary Author	Rita L. Ailinger			
Publication year	2007			
Title	Predictors of Adherence to Latent Tuberculosis Infection Therapy in Latino Immigrants			
Journal	Journal of Community Health Nursing			
Volume	24			
Issue	3			
Pages	191-198			
Note(s)				
Study characteristics				
Study setting	City/Country	Study centre	%foreign born / % study population at risk	Year
	USA	Public Health Clinic	100% foreign born 100% population at risk	2004-2005
Theoretical model	Self-select			
Study design	Descriptive Study			
Data collection	Review of records/data from medical records			
Recruitment method	Randomly selected records from the target population			
Population characteristics	Target population	Sample size		
	Latino immigrants	153		
Demographics				
Age	Mean	Range	Categories	
	26.1	18-56	Not Specified	
Sex	Man 56 (37%), Woman 97 (63%)			
Country of origin	El Salvador 54 (35.3%), Bolivia 27 (17.6%), Guatemala 20 (13.1%), Honduras and Argentina 14 (9.2%), Peru 9 (5.9%), Mexico 4 (2.6%), Costa Rica 3 (2%), Ecuador and Nicaragua 2 (1.3%), Paraguay, Colombia, Brazil and Cuba 1 (0.7%)			
Visa status group	Immigrants			
Years in 'x' country	Range 1-22, Mean 4.58, SD 4.11			
Race/ Ethnicity	Not specified			
Education	Years of education 0-18, mean 10.17 and SD 3.31			
Marital status	Single 82 (54%), Married 57 (37%), Separated 8 (5%) and no information 6 (4%)			
Occupation	Skilled and unskilled 57 (37%), Students 31 (20%), Postpartum mothers 27 (18%) and missing data 38 (25%)			
Socioeconomic status	Not specified			
Religion	Not specified			
Language(s)	Not specified			
Other				
Aim of the study	Examine the Predictors of Adherence to Latent Tuberculosis Infection Therapy in Latino Immigrants at a Public health clinic			
Outcome(s) measured	Adherence to treatment and predictors			
Focus of intervention	Not Applicable			
Number of conditions (including control)	Not Applicable			
Duration of intervention	Not Applicable			
Delivery mode of intervention	Not Applicable			
Primary staff	Not Applicable			
Training provided by	Not Applicable			

Latent TB treatment	Type of medication	Dose	Duration	
	Isoniazid	Not specified	9 months	
Follow-up	Type	Frequency	Duration	Carried out by
	Clinic visits	monthly	8 months	Nurse
Adherence to LTBI treatment				
Definition	Number of doses of Isoniazid taken.			
Measure of adherence	Number of months that the client was present in a clinic appointment and reported taking the INH.			
Measurement tool	Monthly report to clinic appointment. The researchers noted the number of months that patient was adherent.			
Tool validated? If so, how?	Not specified			
Measurement carried out by	Nurse			
Main findings	• The mean number of months adherent was 4.71 (range=0.8, SD=3.1). • Mean number of doses taken was 143 with a range of 0-240 (SD=69) • Adherence dropped off in a linear fashion from month 1(84%) to month 8 (34%). • A total of 52 (34%) patients completed 8 months of LTBI therapy and were given their final month supply. • Fifty-eight clients (38%) reported side effects and of those only four cases (3%) were discontinued with medical device. • No significant correlation between demographics and adherence to treatment were found • Only 2 factors were significantly related to adherence: the occurrence of side effects (r= .212 , p=.015) and the number of different PHNs who saw the client during treatment (r= .646, p≤ .001)			
Limitations	Bias – the sample of the study was somewhat self-selected			

ANNEX IV

Data Charting Form				
Study reference				
Primary Author	Rita L. Ailinger			
Publication year	2010			
Title	The Effect of a Cultural Intervention on Adherence to Latent Tuberculosis Infection Therapy In Latino Immigrants			
Journal	Public Health Nursing			
Volume	27			
Issue	2			
Pages	115-120			
Note(s)				
Study characteristics				
Study setting	City/Country	Study centre	% foreign born / % study population at risk	Year
	USA	Public health Chest Clinic in an urban county of Virginia	100 / 100	Not specified
Theoretical model	N.S.			
Study design	Pre-experimental designed			
Data collection	Self-report and medical chart			
Recruitment method	Convenient sample (Latino immigrants who came to the public health clinic to start LTBI therapy)			
Population characteristics	Target population	Sample size		
	Latino immigrants	53 (intervention) and 131 (historical)		
Demographics				
Age	Mean	Range	Categories	
	Interventional 25.49 Historical 26.25	Not specified	Not Specified	
Sex	Interventional – Female 41 (72%), Historical – 80 (59%) Interventional – Male 18 (28%), Historical – 56 (41%)			
Country of origin	Interventional – Bolivia 20 (38%), El Salvador 15 (28%), Guatemala 7 (13%), Honduras 4 (8%), Argentina 3 (6%), Peru, Mexico and Ecuador 1 (2%) Historical – Bolivia 26 (19%), El Salvador 48 (35%), Guatemala 17 (13%), Honduras, 12 (9%), Argentina 11 (8%), Peru 8 (6%), Mexico 3 (2%), Ecuador, Costa Rica and Nicaragua 2 (1%)			
Visa status group	Not specified			
Years in 'x' country	Interventional 3.83 years in US SD 4.14 and Historical 4.71 years SD 4.30			
Race/ Ethnicity	Not specified			
Education	Interventional 10.69 years SD 3.12 and Historical 10.18 years SD 3.52			
Marital status	Not specified			
Occupation	Interventional – Unskilled 20 (35%), Semiskilled 5 (8%), Skilled 6 (10%) and students 2 (3%) Historical – Unskilled 30 (22%), Semiskilled 1 (7%), Skilled 7 (5%) and students 27 (20%)			
Socioeconomic status	Not specified			
Religion	Not specified			
Language(s)	English and Spanish			
Other				
Aim of the study	Report the Cultural Intervention and the adherence to LTBI treatment among subjects who receive the intervention compared with an historical/ comparison sample			
Outcome(s) measured	Adherence			
Focus of intervention	Cultural intervention			
Number of conditions (including control)	5 components: **1)** Clients saw the same interventionist nurse for each visit **2)** The interventionist nurse inquired about the client's family member before starting care at each			

<table>
<tr><td></td><td colspan="4">monthly clinic visit
3) A common Latino proverb was stated by the interventionist nurse at each clinic visit
4) Latino-adapted educational materials written at the sixth-grade level were given to clients
5) Both the interventionist nurses were fluent in Spanish; one was bicultural / bilingual</td></tr>
<tr><td>Duration of intervention</td><td colspan="4">9 months</td></tr>
<tr><td>Delivery mode of intervention</td><td colspan="4">Action of Nurse</td></tr>
<tr><td>Primary staff</td><td colspan="4">PHN – anthropologist and interventionist nurse</td></tr>
<tr><td>Training provided by</td><td colspan="4">PHN (PI)</td></tr>
<tr><td rowspan="2">Latent TB treatment</td><td>Type of medication</td><td>Dose</td><td colspan="2">Duration</td></tr>
<tr><td>Isoniazid</td><td>Not specified</td><td colspan="2">9 months</td></tr>
<tr><td rowspan="2">Follow-up</td><td>Type</td><td>Frequency</td><td>Duration</td><td>Carried out by</td></tr>
<tr><td>Clinic visits</td><td>monthly</td><td>9 months</td><td>Nurse</td></tr>
<tr><td colspan="5">Adherence to LTBI treatment</td></tr>
<tr><td>Definition</td><td colspan="4">Not specified</td></tr>
<tr><td>Measure of adherence</td><td colspan="4">Self-report of number of pills taken</td></tr>
<tr><td>Measurement tool</td><td colspan="4">Number of pills documented – medical record</td></tr>
<tr><td>Tool validated? If so, how?</td><td colspan="4">Not specified</td></tr>
<tr><td>Measurement carried out by</td><td colspan="4">Not specified</td></tr>
<tr><td>Main findings</td><td colspan="4">• Intervention was efficacious
• Statistically significant difference between the 2 groups. The intervention group took a greater number of pills than the historical/comparison group and the difference was significant, t(85) = 1.94, p =.028.
• Intervention group taking 28 doses (or almost a month’s treatment) more than the historical group</td></tr>
<tr><td>Limitations</td><td colspan="4">Attrition due to medical advice, pregnancy and side effects, sample size and lack of a randomized clinical trial</td></tr>
</table>

ANNEX V

Data Charting Form				
Study reference				
Primary Author	Rachel J Bennett			
Publication year	2014			
Title	Prevalence and Treatment of Latent Tuberculosis Infection Among Newly Arrived Refugees in San Diego County, January 2010–October 2012			
Journal	American Journal of Public Health			
Volume	104			
Issue	4			
Pages	e95-e102			
Note(s)				
Study characteristics				
Study setting	City/Country	Study centre	%foreign born / %study population at risk	Year
	San Diego county, California, USA	San Diego Refugees Health Assessment Program Clinic	100% / 916/4280 (21.4%) were QFT positive, 823/916 (89.9%) were LTBI diagnosed	January 2010 – October 2012
Theoretical model	N.S.			
Study design	N.S.			
Data collection	Data extracted from refugee health electronic information system (RHEIS) database and self-reporting			
Recruitment method	Electronic database and visit to the clinic			
Population characteristics	Target population		Sample size	
	Refugees		Total=4280; prevalence of LTBI in 823 only 373 initiate LTBI treatment	
Demographics				
Age	Mean	Range	Categories	
	Not specified	13-50	13-17; 18-34; 35-49	
Sex	Female =2126, 189 (8.9%) offered treatment, only 142 (75.1%) initiate treatment Male =2154, 300 (13.9%) offered treatment, only 231 (77.0%) initiate treatment			
Country of origin	Middle East = 78.6 initiate treatment Asia = 88.35 initiate treatment Sub-Saharan Africa = 60.5% initiate treatment Others = non initiated treatment, most are from South America			
Visa status group	Refugees			
Years in 'x' country	Newly arrived, maximum of 90 days in San Diago County, California			
Race/ Ethnicity	Not Specified			
Education	0-6 years = 68% 7 – 12 = 77.6% 12 < = 84.7%			
Marital status	Not specified			
Occupation	Not Specified			
Socioeconomic status	Not Specified			
Religion	Not specified			
Language(s)	Not Specified			
Other				
Aim of the study	To determine the prevalence of by birth region and to assess clinical risk factors To identify demographic and clinical factors associated with LTBI treatment initiation and completion among refugees diagnosed with LTBI.			

<table>
<tr><td>Outcome(s) measured</td><td colspan="4">Primary outcome is the diagnosis of LTBI
Secondary outcome is treatment initiation and completion</td></tr>
<tr><td>Focus of intervention</td><td colspan="4">Not Specified</td></tr>
<tr><td>Number of conditions (including control)</td><td colspan="4">Not Specified</td></tr>
<tr><td>Duration of intervention</td><td colspan="4">6 - 9 months</td></tr>
<tr><td>Delivery mode of intervention</td><td colspan="4">Not Specified</td></tr>
<tr><td>Primary staff</td><td colspan="4">Not Specified</td></tr>
<tr><td>Training provided by</td><td colspan="4">Not Specified</td></tr>
<tr><td rowspan="2">Latent TB treatment</td><td>Type of medication</td><td>Dose</td><td colspan="2">Duration</td></tr>
<tr><td>Isoniazid</td><td>Not specified</td><td colspan="2">6 - 9 months</td></tr>
<tr><td rowspan="2">Follow-up</td><td>Type</td><td>Frequency</td><td>Duration</td><td>Carried out by</td></tr>
<tr><td>Not Specified</td><td>Not Specified</td><td>6 - 9 months</td><td>Not Specified</td></tr>
<tr><td colspan="5">Adherence to LTBI treatment</td></tr>
<tr><td>Definition</td><td colspan="4">completion of daily INH for 6 – 9 months</td></tr>
<tr><td>Measure of adherence</td><td colspan="4">Not Specified</td></tr>
<tr><td>Measurement tool</td><td colspan="4">Not Specified</td></tr>
<tr><td>Tool validated? If so, how?</td><td colspan="4">Not specified</td></tr>
<tr><td>Measurement carried out by</td><td colspan="4">Not specified</td></tr>
<tr><td>Main findings</td><td colspan="4">• Treatment completion is significantly more likely among refugees with 7-12 years of education
• Reasons for defaulting treatment were either the patient
o Chose to stop
o Moved out of San Diego</td></tr>
<tr><td>Limitations</td><td colspan="4">• Self-reporting on smoking, diabetes, malignancy, ESRD and education are biased
• Self-reporting results are underreported either because of stigma or previously undiagnosed medical conditions
• The findings are limited only to newly arrived refugees in San Diego, California. As a result do not represent the refugees in USA</td></tr>
</table>

ANNEX VI

Data Charting Form				
Study reference				
Primary Author	Marylyn M. McEwen			
Publication year	2005			
Title	Mexican Immigrants' Explanatory Model of Latent Tuberculosis Infection			
Journal	Journal of Transcultural Nursing			
Volume	16			
Issue	4			
Pages	347-355			
Note(s)				
Study characteristics				
Study setting	City/Country	Study centre	%foreign born / % study population at risk	Year
	Arizona, USA	TB clinic located in US community that borders the Mexican State of Sonora	100% foreign born	Not specified
Theoretical model	Immigrant's explanatory models			
Study design	Ethnographic study.			
Data collection	Multiple methods: a) participant observation b) demographic questionnaire c) participant interviews d) review of medical records			
Recruitment method	By the TB clinic staff			
Population characteristics	Target population		Sample size	
	Immigrants		14	
Demographics				
Age	Mean	Range	Categories	
	Not specified	25-72	Not specified	
Sex	9 males, 5 females			
Country of origin	Mexico			
Visa status group	Immigrants			
Years in 'x' country	From 4 to 45 years with mean of 13 years			
Race/ Ethnicity	Not specified			
Education	Level of education from 3 to 17 years with a mean of 11 years			
Marital status	Majority married			
Occupation	8 participants worked for wages outside the home, 2 retired			
Socioeconomic status	Majority reported barely having enough money to make ends meet			
Religion	Not specified			
Language(s)	English and Spanish			
Other				
Aim of the study	To reveal how the multiple and disparate explanations of latent tuberculosis infection (LTBI) from the U.S. and Mexico professional health sectors and the popular sector are used to inform the explanatory model (EM) of LTBI for Mexican immigrants residing in the U.S.-Mexico border region.			
Outcome(s) measured	Patient's understanding of their illness experience and its meaning			
Focus of intervention	Not Applicable			
Number of conditions (including control)	Not Applicable			
Duration of intervention	Not Applicable			
Delivery mode of intervention	Not Applicable			
Primary staff	Not Applicable			
Training provided by	Not Applicable			
Latent TB treatment	Type of medication	Dose	Duration	

	Not specified	Not specified	Not specified	
Follow-up	Type	Frequency	Duration	Carried out by
	Not specified	Not specified	Not specified	Not specified
Adherence to LTBI treatment				
Definition	Not specified			
Measure of adherence	Not specified			
Measurement tool	Not specified			
Tool validated? If so, how?	Not specified			
Measurement carried out by	Not specified			
Main findings	• For the Mexican Immigrants who participated in the study, their understanding of LTBI was constructed in the context of multiple and conflicting explanations from the popular and professional sectors that are historically unique and foundational to the border region. • The discrepancies between the explanations of LTBI from the US and Mexico professional health sectors contributed to suspicion and distrust of the diagnosis and resulted in participants questioning the veracity of health care providers on both sides of the border.			
Limitations	Not specified			

ANNEX VII

Data Charting Form				
Study reference				
Primary Author	Marylyn Morris McEwen			
Publication year	2007			
Title	Resistance, Health, and Latent Tuberculosis Infection Mexican Immigrants at the U.S. Mexico Border			
Journal	Research and Theory for Nursing Practice			
Volume	21			
Issue	3			
Pages	185-197			
Note(s)				
Study characteristics				
Study setting	City/Country	Study centre	%foreign born / %study population at risk	Year
	Nogales, Arizona, USA	Nogales, Arizona	Not specified	Not specified
Theoretical model	Not specified			
Study design	Critical ethnographic methodology			
Data collection	Multiple methods: a) participant observation b)demographic questionnaire c) participant interviews d)review of medical records			
Recruitment method	Recruited by TB clinical staff member			
Population characteristics	Target population	Sample size		
	Mexican Immigrants	8		
Demographics				
Age	Mean	Range	Categories	
	Not specified	19-40	Not specified	
Sex	Women 100%			
Country of origin	Mexico			
Visa status group	Immigrants			
Years in 'x' country	Ranged from 6 to 22 years with a mean of 14.6 years			
Race/ Ethnicity	Not specified			
Education	Mean numbers of years of formal education was 12.5 ; 2 participants were educated in the US , three in both countries and three in Mexico only			
Marital status	Not specified			
Occupation	4 worked for wages outside the home			
Socioeconomic status	Not specified			
Religion	Not specified			
Language(s)	Spanish and English			
Other				
Aim of the study	To explore how a group of Mexican immigrant women (N = 8) at risk of LTBI treatment failure interpreted and ultimately resisted LTBI preventive treatment.			
Outcome(s) measured	Resistance to medication			
Focus of intervention	Not Applicable			
Number of conditions (including control)	Not Applicable			
Duration of intervention	Not Applicable			
Delivery mode of intervention	Not Applicable			
Primary staff	Not Applicable			
Training provided by	Not Applicable			
Latent TB treatment	Type of medication	Dose	Duration	
	INH	Not specified	9 months	

Follow-up	Type	Frequency	Duration	Carried out by
	Not specified	Not specified	Not specified	Not specified
Adherence to LTBI treatment				
Definition	Not Specified			
Measure of adherence	Not Specified			
Measurement tool	Not Specified			
Tool validated? If so, how?	Not Specified			
Measurement carried out by	Not Specified			
Main findings	• For participants, their interpretations and responses to LTBI treatment extend beyond the concept of treatment adherence. To contextualize the study findings the discussion situated within the perspective of oppression and resistance that is historically rooted in the US-Mexico border region. • The study provides an account of how Mexican immigrant women avoided direct confrontation with health system but nevertheless, through everyday forms of resistance, managed to assert control over choices about their own health and welfare.			
Limitations	Not Specified			

ANNEX VIII

Data Charting Form				
Study reference				
Primary Author	Michael J. Peluso			
Publication year	2014			
Title	Successful Management of Latent Tuberculosis Infection in an Underserved Community by a Student- run Free Clinic			
Journal	Journal of health Care for poor and underserved			
Volume	25			
Issue	2			
Pages	838 - 842			
Note(s)				
Study characteristics				
Study setting	City/Country	Study centre	% foreign born / %study population at risk	Year
	New haven, Connecticut, USA	HAVEN Free Clinic	100 / 100	January 2007– December 2012
Theoretical model	N.S.			
Study design	Retrospective			
Data collection	• Patients assessed for TB exposure and infection by tuberculin skin testing (TST). Patients with a positive TST undergo further evaluation by performing chest X-ray to rule out active TB. Patients diagnosed with LTBI enrollment in the study. • A chart review of the LTBI program to determine the clinical and demographic characteristics of the patients in the program and the INH completion rate.			
Recruitment method				
Population characteristics	Target population	Sample size		
	Underserved foreign-born	39		
Demographics				
	Mean	Range	Categories	
Age	34	21 - 54	Not Specified	
Sex	F= 17 (44%) M= 22 (56%)			
Country of origin	Mexico + 18(46%) Other central/South America= 18(46%) Asia= 1(3%) Caribbean= 1(3%) Africa= 1(3%)			
Visa status group	Not specified			
Years in 'x' country	4 years (0 – 15)			
Race/ Ethnicity	Latino, Asian and Black			
Education	Primary= 19(48%) Secondary= 10(26%) Post-secondary= 6(15%) Not recorded = 4(10%)			
Marital status	Married/ domestic partner = 10(26%) Divorced= 1(3%) Widowed= 1(3%) Not recorded = 3(5%)			
Occupation	Not Specified			
Socioeconomic status	Low socioeconomic			
Religion	Not specified			

Language(s)	Spanish= 36(92%) English = 2(5%) Other = 1(3%)			
Other				
Aim of the study	To evaluate the program developed to provide LTBI treatment to an underserved, high risk, foreign-born population.			
Outcome(s) measured	Patient outcomes: • Program completion was defined by documentation in the medical record that a patient had taken nine months of INH. • Managed discontinuation was defined as discontinuation of LTBI treatment for reasons of poor adherence and/or medication side effects. • Loss to follow‐up was defined as lack of documentation of program completion or discontinuation in the medical record.			
Focus of intervention	TB advocate communicates with his or her patients by phone as needed. In addition, patients can contact their Advocate with questions or concerns. Through frequent contact, the TB Advocate facilitates LTBI therapy and addresses medical and psycho-social issues that arise. TB Advocate investigates adherence barriers by asking a standardized, open- ended question and using a checklist			
Number of conditions (including control)	6 components The TB advocate: **1)** Performs a history and physical examination under the supervision of a senior health professional student and attending clinician. **2)** Enrolls the patient in the program after educating him or her about LTBI and INH therapy **3)** Conducting a clinical screening for contraindications to treatment. **4)** Assess the treatment end-date is recalculated based upon the number of missed doses. **5)** Identifies signs and symptoms of active TB or INH toxicity by conducting a brief symptoms check followed by a physical examination and laboratory studies. **6)** At the visit conclusion, provides education and adherence counseling and addresses other concerns.			
Duration of intervention	9 months			
Delivery mode of intervention	Record using a visual-analog scale			
Primary staff	TB Advocates consists of pre-clinical, Spanish speaking, health professional (medical, nursing, physician assistant) students trained in the clinical knowledge and skills necessary for LTBI management			
Training provided by	A senior medical student and attending medical director administratively manage the program, train, and supervise the TB Advocates.			
Latent TB treatment	Type of medication	Dose	Duration	
	Isoniazid	Not specified	9 months	
Follow-up	Type	Frequency	Duration	Carried out by
	Clinic visits	monthly	9 months	TB advocate
Adherence to LTBI treatment				
Definition	A nine-month course of isoniazid (INH) therapy			
Measure of adherence	Record of patient self-report number of pills taken per month			
Measurement tool	TB Advocate assesses medication adherence using a standardized, structured questionnaire inquiring how many pills have been taken over the last 30 days			
Tool validated? If so, how?	The treatment end-date is recalculated based upon the number of missed doses.			
Measurement carried out by	TB advocates			
Main findings	• Student-run programs could represent an opportunity for the intensive management of this latent disease and education of future providers. • Student- run clinics serving high- risk populations may have the potential to increase access to LTBI therapy and contribute to TB control efforts. • The one-on-one relationship between providers and patients in the program have			

	increased adherence by improving communication and education, and addressing patients' concerns about LTBI and INH therapy • Improved communication through shared language, direct phone access, and a patient-centered interview model have contributed to patient adherence and satisfaction
Limitations	• Patient tracking is difficult in our setting because contact information is not permanent, and many patients reside in our catchment area for a short time • Unable to identify specific risk factors for loss to follow-up due to our small sample size.

ANNEX IX

Data Charting Form				
Study reference				
Primary Author	P. Subedi			
Publication year	2015			
Title	Evaluation of latent tuberculous infection and treatment completion for refugees in Philadelphia, PA, 2010–2012			
Journal	Journal of Tubercle and Lung Diseases			
Volume	19			
Issue	5			
Pages	565 - 569			
Note(s)				
Study characteristics				
Study setting	City/Country	Study centre	% foreign born / % study population at risk	Year
	Philadelphia, USA	8 refugee health centers and non-refugee health centers	100 % / 77.9 % only adults	2010 - 2012
Theoretical model	N.S.			
Study design	Retrospective Cohort study			
Data collection	Data retrieved and collated from three sources: 1) National Electronic Disease Surveillance System (PA-NEDSS) 2) Electronic Disease Notification (EDN) system 3) TB notification forms sent to the PDPH by health care providers			
Recruitment method	Convenient sample (Latino immigrants who came to the public health clinic to start LTBI therapy)			
Population characteristics	Target population	Sample size		
	Newly arrived refugees	n=97 (PRHC clinic) n=52 (non-PRHC clinic)		
Demographics				
Age	Mean	Range	Categories	
	Non Specified	PRHC clinic: adult 77, children 20 Non-PRHC clinic: adult 39, children 13	B1= Extra-pulmonary TB B2 = TST ≥ 10 mm, IGRA positive B3 = Contacts of known active TB case	
Sex	PRHC clinic: male 51, female 46 Non-PRHC clinic: male 29, female 23			
Country of origin	PRHC clinic: Bhutan 68 / Burma 20 / Other countries 9 Non-PRHC clinic: Bhutan 22 / Burma 14 / Other countries 16			
Visa status group	Refugees			
Years in 'x' country	23 days (7 – 734)			
Race/ Ethnicity	Not Specified			
Education	Interventional 10.69 years SD 3.12 and Historical 10.18 years SD 3.52			
Marital status	Not specified			
Occupation	Not Specified			
Socioeconomic status	Not Specified			
Religion	Not specified			
Language(s)	Not Specified			
Other				
Aim of the study	• To compare LTBI evaluation and treatment of refugees at Philadelphia Refugee health Collaborative (PRHC) and non-PRHC clinics to gain a better understanding of the effectiveness of this novel collaborative approach • How it could serve as a model for other communities seeking to improve TB care and better serve refugees			

Outcome(s) measured	Comparison of completion of treatment at PRHC and non-PRHC clinics			
Focus of intervention	Regular culturally appropriate refugee orientation meetings, follow-up patient education meetings and materials to reinforce information communication from the meetings			
Number of conditions (including control)	5 components: **1)** call cases to remind their appointments **2)** call pharmacies to refill medication **3)** Offer bilingual service **4)** Preset visit schedules **5)** regular collaborative meetings to discuss the progress of cases and ensure quick, seamless referrals for services			
Duration of intervention	8 months based on the length of insurance provided by the government			
Delivery mode of intervention	Many parties involved Doctors, nurses, social workers, case workers			
Primary staff	Not specified			
Training provided by	Not specified			
Latent TB treatment	Type of medication	Dose	Duration	
	not specified	Not specified	8 months	
Follow-up	Type	Frequency	Duration	Carried out by
	Clinic visits	Not Specified	8 months	Non specified
Adherence to LTBI treatment				
Definition	Not specified			
Measure of adherence	Not Specified			
Measurement tool	Not Specified			
Tool validated? If so, how?	Not specified			
Measurement carried out by	Not specified			
Main findings	• LTBI treatment completion rates are higher in collaborative PRHC clinics than non-PRHC clinics. • Health screening and follow-up appointments are provided at PRHC clinics by a quick cross-clinic referral system, logistic support from resettlement agencies and easy access to appointments. All these are left to the refugee at non-PRHC clinics. • PRHC clinics can refer refugees for further treatment to TB clinic after the expiration of government insurance where they can receive culturally and linguistically appropriate support. Referrals form non-PRHC clinics are not accepted • Number of LTBI increase from 2010 (13%) to 2012 (49.2%) in Philadelphia			
Limitations	No interviews were conducted with the refugees to assess • Length and content of TB orientation provided at refuges camps before arrival • How effectively the refugees understood the pre-departure screening information			